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(71) Applicant *(for all designated States except US)*: PHARMAGENICS, INC. [US/US]; 4 Pearl Court, Allendale, NJ 07401-1623 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BEUTEL, Bruce, A. [US/US]; 33 BonAire Circle, Apartment 8206, Suffern, NY 10901 (US). SHERMAN, Michael, L [CA/US]; 314 Forest Avenue, Glen Ridge, NJ 07028 (US). COPPOLA, George, R. [US/US]; 5 Holland Place, Hartsdale, NY 10530 (US).

(74) Agents: OLSTEIN, Elliot, M. et al.; Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart, & Olstein, 6 Becker Farm Road, Roseland, NJ 07068-1739 (US).

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(57) Abstract

A method of inhibiting HIV protease function which comprises administering to a host an effective amount of an oligonucleotide which inhibits HIV protease function. Preferred oligonucleotides are RNA oligonucleotides which include at least one of the following oligonucleotide sequences: (a) 5' - GGAAAGUGGAC - 3'; (b) 5' - AANGU - 3'; and (c) 5' - ANUGGA - 3'; (d) 5' - GGAAAGUGGACRRR - 3'; (e) 5' - RGUGAGUGUGGGCR - 3'; (f) 5' - RGUGAGUGUGGGGCR - 3'; (g) 5' - AGUGUG - 3'; (h) 5' - UNGAUNY - 3'; (i) 5' - CCUC - 3'; and (j) 5' - GGUGNA - 3', wherein A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, U is modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, or uracil. The oligonucleotide may include a looped region bounded by a base-paired stem region, and at least a portion of at least one of sequences (a) through (j) is contained in the looped region. Such oligonucleotides bind to HIV protease, thereby inhibiting HIV protease function and preventing HIV maturation.

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OLIGONUCLEOTIDES WHICH INHIBIT HIV PROTEASE FUNCTION

This invention relates to oligonucleotides which may be employed in treating or preventing HIV infection. More particularly, this invention relates to oligonucleotides which inhibit HIV protease function.

Proteolysis is important in the life cycle of Human Immunodeficiency Virus, or HIV. At least some of this proteolysis is carried out by an aspartic protease encoded by HIV, referred to as HIV protease. HIV protease is synthesized as part of the gag-pol polyprotein with other viral proteins. The gag-pol polyprotein dimerizes, providing enough protease activity to provide autolytic cleavage in trans to free the protease domain from the pol region of the polyprotein. The 11 kDa protease forms dimers which are active in vivo and in vitro. HIV protease is necessary for HIV maturation. After the immature virus has budded off from an infected cell, the protease cleaves gag and gag-pol polyproteins to generate four structural proteins of the virion core, as well as reverse transcriptase, integrase, and protease. (Ratner, et al., Nature, Vol. 313, pgs. 277-284 (1985); Wain-Hobson, et al., Cell, Vol. 40, pgs. 9-17 (1985); Graves, et al., Proc. Nat. Acad. Sci., Vol. 85, pgs. 2449-2453 (1988); Kay, et al., Biochimica et Biophysica Acta, Vol. 1048, pgs. 1-18

(1990); Gottlinger, et al., Proc. Nat. Acad. Sci., Vol. 86, pgs. 5781-5785 (1990)). The activity of HIV protease is necessary for the spread of HIV within an infected individual.

A number of inhibitors of HIV protease have been identified. Most of these inhibitors are peptides or peptide analogues. (Meek, et al., Nature, Vol. 343, pgs. 90-92 (1990); McQuade, et al., Science, Vol. 247, pgs. 454-456 (1990); Roberts, et al., Science, Vol. 248, pgs. 358-361 (1990); Ashorn, et al., Proc. Nat. Acad. Sci., Vol. 87, pgs. 7472-7476 (1990)).

As a proteolytic enzyme, it is unexpected that HIV protease should exhibit tight binding to specific oligonucleotides. It has been discovered that HIV protease binds tightly to nucleic acids and specific sequences governing this binding have been identified.

It is an object of the present invention to provide oligonucleotides which inhibit the function of HIV protease. Such oligonucleotides would be advantageous over peptide inhibitors of HIV protease in that the oligonucleotides can be variously modified for therapeutic use, or such oligonucleotides can be produced via expression vector systems in HIV-infected cells to prevent viral maturation and spread of the virus, or in non-infected cells to prevent HIV infection.

In accordance with an aspect of the present invention, there is provided a method of inhibiting HIV protease function. The method comprises contacting HIV protease with an effective amount of an oligonucleotide, or a molecule containing such an oligonucleotide, which inhibits HIV protease function.

The term "inhibiting HIV protease function", as used herein, means that the oligonucleotide prevents HIV protease from performing its functions, preferably by binding to HIV protease. Such functions include, but are

not intended to be limited to, the cleavage of HIV proteins as hereinabove described. It is also believed that HIV protease may bind to its own gene and/or to other sites in the viral genome. The binding of HIV protease to sites in the viral genome may be important for packaging small amounts of protease which may be used to initiate the original cleavage of the gag-pol polyprotein to release free protease upon viral gene activation. Thus, HIV protease activity may be regulated positively or negatively by virtue of the binding of HIV protease to one or more sites in the HIV genome. Although the scope of the present invention is not to be limited to any theoretical reasoning, it is believed that the oligonucleotides may block proteolysis by inhibiting HIV protease activity directly, (either by interfering with the catalytic activity of the enzyme or by interfering with dimerization of the two subunits of the enzyme, such dimerization being necessary for protease activity) or by preventing the binding of HIV protease to one or more sites in the HIV genome. The term "inhibiting" as used herein means inhibiting one or more of the foregoing functions.

The term "oligonucleotide" as used herein means that the oligonucleotide may be a ribonucleotide; i.e., an RNA oligonucleotide; a deoxyribonucleotide; i.e., a DNA oligonucleotide; or a mixed ribonucleotide/deoxyribonucleotide; i.e., the oligonucleotide may include ribose or deoxyribose sugars, 2'-O-methyl ribose or other 2'-O-conjugated sugars, or a mixture of such sugars. Alternatively, the oligonucleotide may include other 5-carbon or 6-carbon sugars, such as, for example, arabinose, xylose, glucose, galactose, or deoxy derivatives thereof or any mixture of sugars.

The phosphorus-containing moieties of the oligonucleotides of the present invention may be modified or unmodified. The phosphorus-containing moiety may be,

for example, a phosphate, phosphonate, alkylphosphonate, aminoalkyl phosphonate, alkyl-thiophosphonate, phosphoramidate, phosphorodiamidate, phosphorothioate, phosphorodithioate, phosphorothionate, phosphorothiolate, phosphoramidothiolate, and phosphorimidate. It is to be understood, however, that the scope of the present invention is not to be limited to any specific phosphorus moiety or moieties. Also, the phosphorus moiety may be modified with a cationic, anionic, or zwitterionic moiety. The oligonucleotides may also contain backbone linkages which do not contain phosphorus, such as carbonates, carboxymethyl esters, acetamidates, carbamates, acetals, and the like. The oligonucleotides may also contain the backbone linkage of peptide nucleic acids. (Egholm, et al., J. Am. Chem. Soc., Vol. 114, pgs. 1895-1897 (1992)).

The oligonucleotides also include any natural or unnatural, substituted or unsubstituted, purine or pyrimidine base. Such purine and pyrimidine bases include, but are not limited to, natural purines and pyrimidines such as adenine, cytosine, thymine, guanine, uracil, or other purines and pyrimidines, or analogs thereof, such as isocytosine, 6-methyluracil, 4,6-di-hydroxypyrimidine, hypoxanthine, xanthine, 2,6-diaminopurine, 5-azacytosine, 5-methyl cystosine, 7-deaza-adenine, 7-deaza-guanine, and the like.

The oligonucleotides may be modified such that at least one nucleotide unit of the oligonucleotides may include a conjugate group. Such conjugate groups include, but are not limited to, (a) amino acids, including D-amino acids and L-amino acids; (b) peptides, polypeptides, and proteins; (c) dipeptide mimics; (d) sugars; (e) sugar phosphates; (f) neurotransmitters; (g) hormones; (h) poly (hydroxypropylmethacrylamide); (i) polyethylene imine; (j) dextrans; (k) polymaleic anhydride; (l) cyclodextrins; (m) starches; (n) steroids, including sterols such as, but not

limited to, cholesterol; (o) acridine; (p) vitamins; and (q) polyalkylene glycols, such as polyethylene glycol. Such moieties may make the oligonucleotides more resistant to degradation in cells and in the circulation, and/or make the oligonucleotides more permeable to cells and viral particles. The conjugate moiety may be attached to the 3' terminal nucleotide unit and/or the 5' terminal nucleotide unit and/or to an internal nucleotide unit(s), or conjugate moieties may be attached to two or more nucleotide units at the 3' end and/or the 5' end of the oligonucleotide. In one embodiment, substituted nucleotide units may alternate with unsubstituted nucleotide units. In another embodiment, all of the nucleotide units are substituted with a conjugate moiety.

The conjugate moiety may be attached to the oligonucleotide at the purine or pyrimidine base, at the phosphate group, or to the sugar.

When the conjugate moiety is attached to the base, it is preferably attached at certain positions of the base, depending upon the base to which the moiety is attached. When the moiety is attached to adenine, it may be attached at the C2, N6, or C8 positions. When the moiety is attached to guanine, it may be attached at the N2 or C8 positions. When the moiety is attached to cytosine, it may be attached at the C5 or N4 positions. When the moiety is attached to thymine or uracil, it may be attached at the C5 position.

In one embodiment, the oligonucleotide includes from about 5 to about 100 nucleotide units, preferably from about 8 to about 60 nucleotide units.

In one embodiment, the oligonucleotide has no greater than 25% of its bases which are cytosine residues, and preferably no greater than 20% of its bases are cytosine residues. More preferably, no greater than 15% of the bases of the oligonucleotide are cytosine residues.

In yet another embodiment, the oligonucleotide represents a portion of a larger molecule which contains non-oligonucleotide components, such as, for example, peptides or proteins, or simple carbohydrates, and lipids.

In a preferred embodiment, the oligonucleotide is an RNA oligonucleotide which includes at least one of the following sequences:

(a) 5′ - GGAAAGUGGAC - 3′;
(b) 5′ - AANGU - 3′;
(c) 5′ - ANUGGA - 3′,
(d) 5′ - GGAAAGUGGACRRR - 3′;
(e) 5′ - RGUGAGUGUGGGCR - 3′;
(f) 5′ - RGUGAGUGUGGGGCR - 3′;
(g) 5′ - AGUGUG - 3′;
(h) 5′ - UNGAUNY - 3′;
(i) 5′ - CCUC - 3′; and
(j) 5′ - GGUGNA - 3′,

wherein A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, U is modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, or uracil. Such sequences (a) through (j) are sometimes hereinafter referred to as binding sequences.

Applicant has found that certain RNA oligonucleotides which include at least one of the above-mentioned binding sequences (a) through (j) will bind to HIV protease, thereby inhibiting HIV protease function. Representative examples of such oligonucleotides fall into three classes, known as Classes A, B, and C. The sequences of Class A are as follows:

(i) 5′-
GGGAGAAGUAGUGUAGGAAUUCCUCACUAGUGGAUCUUACAUUGGAUUAUAAGGCC-
UGGGUUGUGGCUACCAAGUGUUCAGGCUCGAGAGGUCACAGU-3′;

(ii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAAGAAGGUAUACCUCACUUUCAUCAUCGCACCUG-
UGAGCGGUGUCUUAAUUGUCGUAGGCUCGAGAGGUCACAGU-3';
(iii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAGCCUAUAAGGUCGCCUAGAUUCUUGUUCCUGCU-
GUCUUGAGUUGGAAAGUGGACGUAGCCUCGAGAGGUCACAGU-3';
(iv) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGAGGGAAAGUGGACGGGUCAGGCGCUUACAAUG-
UUACUUUCUUCUACUAAGGUUUUGCCCUCGAGAGGUCACAGU-3';
(v) 5'-
GGGAGAAGUAGUGUAGGAAUUCUAGCGGAAAGUGGACAAAGUUGAGAAUGGAGCUC-
CCAUGCAGAUUAAUCGCGCNUUGGUCUCGAGAGGUCACAGU-3';
(vi) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGCAGGUCUGAACGCAGAGUAGAAAUGGUGUUGG-
UAGUGAAUAAAGAAGUGUGUGCUGGCCUCGAGAGGUCACAGU-3';
(vii) 5'-
GGGAGAAGUAGUGUAGGAAUUCGUUAGUUAAAGUUAGUUUGGUGUAGUGUAUUGGA-
AGUCGAUUUGAAUGCUAGCUGUGGACUCGAGAGGUCACAGU-3';
(viii) 5'-
GGGAGAAGUAGUGUAGGAAUUCACUGGAGGGUUGCUAUAAUCGGGUGAGUGUGGGCAC-
GAUUAUAGUAAGACGCGAGGGCUGCUCGAGAGGUCACAGU-3';
(ix) 5'-
GGGAGAAGUAGUGUAGGAAUUCAUCUGUUCCGUGCACGGAGUCAUAACAAACUCAC-
CUGUCUCGAGUGGAAAGUGGACGCAGCUCGAGAGGUCACAGU-3';
(x) 5'-
GGGAGAAGUAGUGUAGGAAUUCAAUAAGUUGGGAAAGUGGACGAACGGCUGGAGAU-
GGCUUACUCACUUCUUUCGUGCUUGCCUCGAGAGGUCACAGU-3'; and
(xi) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGCUAAUUUCAAGUCAGUUGCGCGGGAAAGUGGA-
CGAACGUUGCAAUGUUGAUCCGGUGGCUCGAGAGGUCACAGU-3'.

Such oligonucleotides are sometimes hereinafter referred to as oligonucleotides (i) through (xi), respectively. Portions of the above oligonucleotides may be primer or flanking sequences.

The sequences of Class B are as follows:

(xii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAGGCAGUGGGGAAGUGAGUGUGGGGCGUCUCUAC-
UUAGUGUGCGAUCAAGCGUACGGCUCGAGAGGUCACAGU-3';
(xiii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAAAGCCUCAACGCUAGGUUGCGUUUAGGGAGCC-
AAGUAGUGAGUGUGGGCGACUAGGGCUCGAGAGGUCACAGU-3'; and
(xiv) 5'-
GGGAGAAGUAGUGUAGGAAUUCGCACACGCAAUGCCAAAGUAGGGAUGUUGCGUCA-
CGGUCUUGGGGAGUGAGAGUGGGCGCCUCGAGAGGUCACAGU-3'.

Such oligonucleotides are sometimes hereinafter referred to as oligonucleotides (xii) through (xiv), respectively. Portions of the above oligonucleotides may be primer or flanking sequences.

The sequences of Class C are as follows:

(xv) 5'-
GGGAGAAGUAGUGUAGGAAUUCAACUUUACUAUUAAACCGCGACGCCUUUUCAGGA-
UAACAAAUGAAUUGGCGGCCCUCUAGCUCGAGAGGUCACAGU-3';
(xvi) 5'-
GGGAGAAGUAGUGUAGGAAUUCCUGAAGUUGGUUUGUUGUUUGUUUUGAUAUAUCC-
AUAGAGAUAUCAGUUUGAGGUUGGUCUCGAGAGGUCACAGU-3';
(xvii) 5'-
GGGAGAAGUAGUGUAGGAAUUCUACGUGGAUAGGUAGAUGGAGAGAUGAUAGUGGU-
GUAACGUUUGAGAUUAAGGGUGCGACUCGAGAGGUCACAGU-3';
(xviii) 5'-
GGGAGAAGUAGUGUAGGAAUUCCCGUCCUCUUCCGGAGGUUUGCUUAGAGGCAUAG-
CUAUCAAAUCGAUACUUAUGGCGCACCUCGAGAGGUCACAGU-3'; and
(xix) 5'-
GGGAGAAGUAGUGUAGGAAUUCUAAGUCCGGUCUAUCGCCUCCUGUACAUGGAUCC-
CAAGGUGAAUACUCGCUUGAUGUCCUCGAGAGGUCACAGU-3'.

Such oligonucleotides are sometimes hereinafter referred to as oligonucleotides (xv) through (xix), respectively. Portions of the above oligonucleotides may be primer or flanking sequences.

Alternatively, the oligonucleotide is a DNA oligonucleotide which includes at least one of the following binding sequences:

(k) 5'-GGAAAGTGGAC-3';

(l) 5'-AANGT-3';

(m) 5'-ANTGGA-3',

(n) 5'-GGAAAGTGGACRRR-3';

(o) 5'-RGTGAGTGTGGGCR-3';

(p) 5'-RGTGAGTGTGGGGCR-3';

(q) 5'-AGTGTG-3';

(r) 5'-TNGATNY-3';

(s) 5'-CCTC-3'; and

(t) 5'-GGTGNA-3'.

wherein A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, T is modified or unmodified thymine or modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, thymine, or uracil

Representative examples of DNA oligonucleotides which include at least one of binding sequences (k) through (t) fall into three classes, known as Classes D, E, and F. The sequences of Class D are as follows:

(xx) 5'-
GGGAGAAGTAGTGTAGGAATTCCTCACTAGTGGATCTTACATTGGATTATAAGGCC-
TGGGTTGTGGCTACCAAGTGTTCAGGCTCGAGAGGTCACAGT-3';

(xxi) 5'-
GGGAGAAGTAGTGTAGGAATTCAAGAAGGTATACCTCACTTTCATCATCGCACCTG-
TGAGCGGTGTCTTAATTGTCGTAGGCTCGAGAGGTCACAGT-3';

(xxii) 5'-
GGGAGAAGTAGTGTAGGAATTCAGCCTATAAGGTCGCCTAGATTCTTGTTCCTGCT-
GTCTTGAGTTGGAAAGTGGACGTAGCCTCGAGAGGTCACAGT-3';

(xxiii) 5'-
GGGAGAAGTAGTGTAGGAATTCTGAGGGAAAGTGGACGGGTCAGGCGCTTACAATG-
TTACTTTCTTCTACTAAGGTTTTGCCCTCGAGAGGTCACAGT-3';

(xxiv) 5'-
GGGAGAAGTAGTGTAGGAATTCTAGCGGAAAGTGGACAAAGTTGAGAATGGAGCTC-
CCATGCAGATTAATCGCGCNTTGGTCTCAGAGAGGTCACAGT-3';
(xxv) 5'-
GGGAGAAGTAGTGTAGGAATTCTGCAGGTCTGAACGCAGAGTAGAAATGGTGTTGG-
TAGTGAATAAAGAAGTGTGTGCTGGCCTCGAGAGGTCACAGT-3';
(xxvi) 5'-
GGGAGAAGTAGTGTAGGAATTCGTTAGTTAAAGTTAGTTTGGTGTAGTGTATTGGA-
AGTCGATTTGAATGCTAGCTGTGGACTCGAGAGGTCACAGT-3';
(xxvii) 5'-
GGGAGAAGTAGTGTAGGAATTCACTGGAGGGTTGCTATAATCGGGTGAGTGTGGGCAC-
GATTATAGTAAGACGCGAGGGCTGCTCGAGAGGTCACAGT-3';
(xxviii) 5'-
GGGAGAAGTAGTGTAGGAATTCATCTGTTCCGTGCACGGAGTCATAACAAACTCAC-
CTGTCTCGAGTGGAAAGTGGACGCAGCTCGAGAGGTCACAGT-3';
(xxix) 5'-
GGGAGAAGTAGTGTAGGAATTCAATAAGTTGGGAAAGTGGACGAACGGCTGGAGAT-
GGCTTACTCACTTCTTTCGTGCTTGCCTCGAGAGGTCACAGT-3'; and
(xxx) 5'-
GGGAGAAGTAGTGTAGGAATTCTGCTAATTTCAAGTCAGTTGCGCGGGAAAGTGGA-
CGAACGTTGCAATGTTGATCCGGTGGCTCGAGAGGTCACAGT-3'.

Such oligonucleotides are sometimes hereinafter referred to as oligonucleotides (xx) through (xxx), respectively. Portions of the above oligonucleotides may be primer or flanking sequences.

The sequences of Class E are as follows:

(xxxi) 5'-
GGGAGAAGTAGTGTAGGAATTCAGGCAGTGGGGAAGTGAGTGTGGGGCGTCTCTAC-
TTAGTGTGCGATCAAGCGTACGGCTCGAGAGGTCACAGT-3';
(xxxii) 5'-
GGGAGAAGTAGTGTAGGAATTCAAAGCCTCAACGCTAGGTTGCGTTTAGGGAGCC-
AAGTAGTGAGTGTGGGCGACTAGGGCTCGAGAGGTCACAGT-3'; and
(xxxiii) 5'-
GGGAGAAGTAGTGTAGGAATTCGCACACGCAATGCCAAAGTAGGGATGTTGCGTCA-
CGGTCTTGGGGAGTGAGAGTGGGCGCCTCGAGAGGTCACAGT-3'.

Such oligonucleotides are sometimes hereinafter referred to as oligonucleotides (xxxi) through (xxxiii), respectively. Portions of the above oligonucleotides may be primer or flanking sequences.

The sequences of Class F are as follows:

(xxxiv)
GGGAGAAGTAGTGTAGGAATTCAACTTTACTATTAAACCGCGACGCCTTTTCAGGATAA
CAAATGAATTGGCGGCCCTCTAGCTCGAGAGGTCACAGT-3';

(xxxv)
GGGAGAAGTAGTGTAGGAATTCCTGAAGTTGGTTTGTTGTTTGTTTTGATATATCCATA
GAGATATCAGTTTGAGGTTGGTCTCGAGAGGTCACAGT-3';

(xxxvi)
GGGAGAAGTAGTGTAGGAATTCTACGTGGATAGGTAGATGGAGAGATGATAGTGGTGTA
ACGTTTGAGATTAAGGGTGCGACTCGAGAGGTCACAGT-3';

(xxxvii)
GGGAGAAGTAGTGTAGGAATTCCCGTCCTCTTCCGGAGGTTTGCTTAGAGGCATAGCTA
TCAAATCGATACTTATGGCGCACCTCGAGAGGTCACAGT-3'; and

(xxxviii)
GGGAGAAGTAGTGTAGGAATTCTAAGTCCGGTCTATCGCCTCCTGTACATGGATCCCAA
GGTGAATACTCGCTTGATGTCCTCGAGAGGTCACAGT-3'.

Such oligonucleotides are sometimes hereinafter referred to as oligonucleotides (xxxiv) through (xxxviii), respectively. Portions of the above oligonucleotides may be primer or flanking sequences.

It is to be understood, however, that the scope of the present invention is not to be limited to the above-mentioned oligonucleotides.

The oligonucleotides may be in the form of a single strand, a double strand, a stem-loop structure, a pseudoknot, or a closed, circular structure. In one embodiment, the ends of the oligonucleotide may be bridged by non-nucleotide moieties. Examples of non-nucleotide bridging moieties include, but are not limited to, those having the following structural formula:

T_1-R-T_2, whereas each of T_1 and T_2 independently is attached to a nucleotide phosphate moiety or a hydroxyl moiety. R is selected from the group consisting of (a) saturated and unsaturated hydrocarbons; (b) polyalkylene glycols; (c) polypeptides; (d) thiohydrocarbons; (e) polyalkylamines; (f) polyalkylene thioglycols; (g) polyamides; (h) disubstituted monocyclic or polycyclic aromatic hydrocarbons; (i) intercalating agents; (j) monosaccharides; and (k) oligosaccharides; or mixtures thereof. In one embodiment, the non-nucleotide bridging moiety may be a polyalkylene glycol such as polyethylene glycol.

In another embodiment, one or more of the non-nucleotide moieties R may be substituted for one or more of the nucleotide units in the HIV protease binding sequences, as hereinabove mentioned.

In one embodiment, the oligonucleotide includes a looped region bounded by a double-stranded base-paired stem region. At least a portion of at least one of sequences (a) through (t) hereinabove mentioned is contained within the looped region. Preferably, all of at least one of sequences (a) through (t) is contained within the looped region.

As an illustrative embodiment, Applicant, by employing the folding analysis program of Zuker (Science, Vo. 244, pgs. 48-52 (1989)), has derived a predicted structure for oligonucleotide (v) in which oligonucleotide (v) has a looped region bounded by a double-stranded hydrogen-bonded stem region. Sequence (d) is contained in the looped region. The predicted structure of oligonucleotide (v) is shown in Figure 1. Similarly, oligonucleotide (xii), which contains sequence (f), is shown in Figure 2. As with sequence (d) in oligonucleotide (v), sequence (f) is contained in a looped region of oligonucleotide (xii).

Also, in general, the oligonucleotides of Class A and Class B contain one of sequences (a) through (d) or (f), respectively, in a looped region as shown in Figure 3. Although the scope of the present invention is not to be limited to any theoretical reasoning, Applicant believes that the preferred oligonucleotides which Applicant has found will bind to HIV protease have a looped region bounded by a hydrogen-bonded stem region in which at least a portion of at least one of sequences (a) through (t) is found in the looped region. It is to be understood, however, that the scope of the present invention is not to be limited to any specific oligonucleotide structure.

The oligonucleotides are administered to a host, such as a human or non-human animal host, in an amount effective to inhibit HIV protease function. Thus, the oligonucleotides may be used to treat or prevent HIV infection. Preferably, the oligonucleotides are administered to a host so as to provide a concentration of oligonucleotide in the blood of from about 10 nanomolar to about 500 micromolar, preferably from about 5 micromolar to about 100 micromolar. It is also contemplated that the oligonucleotides may be administered <u>in vitro</u> or <u>ex vivo</u> as well as <u>in vivo</u>.

The oligonucleotides may be synthesized by a variety of accepted means known to those skilled in the art. For example, the oligonucleotides may be synthesized on an automated nucleic acid synthesizer. Alternatively, the oligonucleotides may be synthesized enzymatically through the use of flanking or primer sequences at the 5' and 3' ends. In another alternative, the oligocucleotides may be synthesized by solution phase chemistry.

It is to be understood, however, that the scope of the present invention is not to be limited to any particular means of synthesis.

The oligonucleotides may be administered in conjunction with an acceptable pharmaceutical carrier as a pharmaceutical composition. Such pharmaceutical compositions may contain suitable excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Such oligonucleotides may be administered by intramuscular, intraperitoneal, intraveneous, or subdermal injection in a suitable solution. Preferably, the preparations, particularly those which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees and capsules, and preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration parenterally or orally, and compositions which can be administered buccally or sublingually, including inclusion compounds, contain from about 0.1 to 99 percent by weight of active ingredients, together with the excipient. It is also contemplated that the oligonucleotides may be administered topically.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself well known in the art. For example, the pharmaceutical preparations may be made by means of conventional mixing, granulating, dragee-making, dissolving or lyophilizing processes. The process to be used will depend ultimately on the physical properties of the active ingredient used.

Suitable excipients are, in particular, fillers such as sugar, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch or paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl

cellulose, hydroxypropylmethylcellulose, sodium carboxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches as well as carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are flow-regulating agents and lubricants, such as, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores may be provided with suitable coatings which, if desired, may be resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, are used. Dyestuffs and pigments may be added to the tablets of dragee coatings, for example, for identification or in order to characterize different combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the oligonucleotide in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin,

or liquid polyethylene glycols. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols, or higher alkanols. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble or water-dispersible form. In addition, suspensions of the active compounds as appropriate oil injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

Additionally, the compounds of the present invention may also be administered encapsulated in liposomes, wherein the active ingredient is contained either dispersed or variously present in corpuscles consisting of aqueous concentric layers adherent to lipidic layers. The active ingredient, depending upon its solubility, may be present both in the aqueous layer, in the lipidic layer, or in what is generally termed a liposomic suspension. The hydrophobic layer, generally but not exclusively, comprises phospholipids such as lecithin and sphingomycelin, steroids

such as cholesterol, surfactants such as dicetylphosphate, stearylamine, or phosphatidic acid, and/or other materials of a hydrophobic nature. The diameters of the liposomes generally range from about 15 nm to about 5 microns.

The oligonucleotides may also be employed as diagnostic probes for determining the presence of HIV protease, and thereby determining HIV infection. In such embodiments, a modified or unmodified oligonucleotide of the present invention is added to a sample suspected of containing HIV protease. The oligonucleotide may be labeled with a detectable marker such as a radioactive label, a chromogen, or an enzyme label. Thus, the oligonucleotide may be employed in a variety of assay methods for the detection of HIV protease, such methods including sandwich assays, competitive assays, ELISA assays, inhibition assays, and other assays known to those skilled in the art.

HIV protease binding sequences may also be administered to a host as part of a gene therapy procedure. For example, an expression vector which includes or encodes a nucleic acid containing the HIV protease-binding sequence of the present invention may be administered to cells of an HIV-infected individual. In one embodiment, such included DNA or RNA sequence has from about 50 to 1,000 or more nucleotide units, preferably from about 150 to about 500 nucleotide units. In one embodiment, the expression vector may include a DNA or RNA sequence which, when transcribed, produces an RNA which binds HIV protease in such a way as to inhibit its function. Examples of expression vectors which may be employed include, but are not limited to, prokaryotic vectors, eukaryotic vectors, and viral vectors, such as retroviral vectors, Herpes virus vectors, adenoviral vectors, and adeno-associated viral vectors. Examples of retroviral vectors include those derived from

Moloney Murine Leukemia Virus, Rous Sarcoma Virus, and Harvey Sarcoma Virus.

Upon reception of the HIV protease-binding oligonucleotide or an expression vector containing a binding sequence by the infected cell, HIV protease function will be inhibited, thereby preventing virus maturation.

In another embodiment, the HIV protease-binding oligonucleotide or an expression vector containing a binding sequence may be administered to a cell in order to prevent HIV infection of the cell. For example, the oligonucleotide or an RNA or DNA encoding a sequence containing the oligonucleotide may be administered to hematopoietic and/or immune stem cells and/or neural cells in order to prevent such cells from undergoing productive HIV infection. Administration of such DNA or RNA can be by any of a number of procedures known to those skilled in the art, including, but not limited to, transfection, electroporation, lipofection, transformation, or transduction with eukaryotic expression vectors such as viruses, including retroviruses, Herpes viruses, adenoviruses, and adeno-associated viruses. Heterologous or autologous transplants of such cells may be administered to HIV patients by procedures known to those skilled in the art.

Administering an expression vector containing a binding sequence to hematopoietic and/or immune stem cells and/or neural cells may interfere with normal function of the stem cells if expression or presence of the oligonucleotide is at high levels, which may be the case if the oligonucleotide is placed under the control of a strong promoter. Thus, expression of the oligonucleotide can be regulated by a tat activation region, or tar sequence. Such sequences are under control of the HIV tat protein. Thus, cells can be carrying an expression vector

encoding the oligonucleotide under the control of a tar element, and production of RNA containing the binding sequence will occur only upon infection of the cell with HIV and production of tat protein (which is essential for viral activation). Thus, a cell will be able to function normally in the absence of the production of large amounts of the oligonucleotide until and unless HIV infection of the cell occurs. Other combinations of regulatory regions and activating factors can be used in place of a tar region and tat protein, respectively.

The oligonucleotides also may be employed in screening compounds for the ability to inhibit HIV protease. In such a screening method, a predetermined amount of HIV protease is contacted with a predetermined amount of an oligonucleotide which binds HIV protease in a first reaction. The amount of HIV protease bound by the oligonucleotide then is determined.

In a second reaction, the predetermined amount of HIV protease is contacted with the predetermined amount of the oligonucleotide which binds HIV protease, and with a predetermined amount of the compound being screened for the ability to inhibit HIV protease. The amount of HIV protease bound by the oligonucleotide in the second reaction then is determined. By comparing the amount(s) of HIV protease bound by the oligonucleotide in the first reaction with the amount of HIV protease bound by the oligonucleotide in the second reaction, the ability of the compound being screened to inhibit HIV protease may be determined.

The oligonucleotides also may be employed in determining HIV infection in an individual. In such a method, a sample (such as, for example, a blood sample) obtained from a person suspected of being infected with HIV, is contacted with an oligonucleotide which binds to HIV protease. The amount of oligonucleotide bound by HIV

protease in the sample then is determined. In one embodiment, the sample is placed on a solid support having a binder for HIV protease. The binder is contacted with the sample for a period of time sufficient to allow HIV protease to bind to the binder. The binder-HIV protease complex then is contacted with an oligonucleotide which binds HIV protease. The oligonucleotide also is conjugated with or bound to a detectable label, such as an enzyme label or a chromogenic label. Upon binding of the labeled oligonucleotide to the binder-HIV protease complex, the amount of bound HIV protease may be determined by measuring the amount of bound label.

The invention will now be described with respect to the following examples; however, the scope of the present invention is not intended to be limited thereby.

Example 1

Binding Studies

The affinity of HIV protease for various RNA molecules was measured by a nitrocellulose filter binding assay. HIV protease was incubated at room temperature for 30 minutes in the presence of ^{32}P end-labeled RNA. The incubation was in a total volume of 20 ul, with 50 mM MES pH6.5, 0.5 mM EDTA, 0.2 mM DTT, 150 mM NaCl, 3mM $MgCl_2$, 2% glycerol, and various concentrations of HIV protease. Under these conditions, protease is in vast (>100-fold) excess over RNA, so the binding is driven by the protease concentration. After incubation, the protease-bound RNA was trapped by filtration through a nitrocellulose filter, and washed with 10 ml reaction buffer. Nitrocellulose filters were dried and the bound radioactive RNA was counted in a scintillation counter. The fraction of initial RNA bound to the filter was compared for the different RNA species. Figure 4 shows the relative binding

affinities for eight different RNA oligonucleotides. One of these (called "Random") is a population of RNA in which there are 60 randomly synthesized bases in the region between two fixed flanking sequences. The flanking sequence at the 5' end has the following sequence:

5'-GGGAGAAGUAGUGUAGGAAUUC-3'.

The flanking sequence at the 3' end has the following sequence:

5'-CUCGAGAGGUCACAGU-3'.

Other oligonucleotides not listed in Classes A, B, and C also have been shown to have significant binding affinity for HIV protease. A common characteristic of these oligonucleotides is that less than 20% of the nucleotide residues of the oligonucleotides are cytosine residues, and they have intermediate affinity between the tight binding oligonucleotides specified herein and the weaker binding random sequences.

Example 2

The GenBank genomic RNA sequences of HIV-1 and HIV-2 were searched for sequences similar to 5'-GGAAAGUGGAC-3' and 5'-GGAAAGUGGACRRR-3' (sequences (a) and (d)). An example of one of the best matches in HIV-1 (12 of 14 nucleotides identical to sequence (d)) is shown in Figure 5. The sequence which is shown in Figure 5 has a structure as predicted by the Zuker method for this region of HIV-1 RNA. (Please note that GenBank employs T in place of U even though the sequence shown in Figure 5 is an RNA.) This particular region of HIV-1 RNA is highly conserved (and is also in the coding region for the HIV-1 vif gene), so that every HIV isolate sequence in the GenBank includes this region. There are other sites in the HIV-1 and HIV-2 genomes which have 8 or 9 of the 11 bases of sequence (a). HIV-2 has one site which has 10 of the 11 bases of sequence (a). Each of these sites is potentially important functionally in the HIV infectious cycle, as HIV protease

may bind to such sequences for some regulatory reason. Thus, oligonucleotides including such sequences may compete with such sequences in the HIV genome for binding to HIV protease, thereby inhibiting HIV protease function.

Alternatively, oligonucleotides complementary to HIV genomic protease binding sites may be used to disrupt the interaction between HIV protease and the genomic RNA.

Example 3

Inhibition of HIV Protease Activity by Oligonucleotides

The ability of RNA sequences to inhibit the proteolytic activity of HIV-1 protease was assayed. The intermediate filament protein vimentin is a natural substrate cleaved by HIV protease. (Shoeman, et al., Proc. Nat. Acad. Sci., Vol. 87, pgs. 6336-6340 (1990)). Intact vimentin has an apparent molecular weight of 57 kDa in SDS/PAGE electrophoresis, and its major initial proteolytic product migrates as 50 kDa. The rate of full-sized vimentin degradation and rate of cleavage product formation were measured in the presence or absence of different RNA sequences at various concentrations.

Reactions contained 300 ng vimentin (final concentration = 370 nM) and 40 nM HIV-1 protease (strain NY5, Bachem Bioscience, Inc.) in a buffer containing 50 mM MES, pH 6.5, 120 mM NaCl, 3 mM $MgCl_2$, 0.9 mM EDTA, 1 mM DTT, and 2% glycerol. Total reaction volume was 15 microliters, and reactions were incubated for one hour at 25°C followed by addition of SDS/PAGE loading buffer, 5 minute incubation at 96°C and SDS/PAGE analysis. Substrate and cleavage products were visualized by silver staining. Figure 6 shows the results of incubation with 40 nM or 100 nM (lanes 3 and 4) RNA oligonucleotide (xii), resulted in significant inhibition of proteolysis compared to the addition of no oligonucleotide (lane 2) or as much as 5000 nM random sequence RNA oligonucleotide of the same length

(lanes 5 and 6). Lane 1 shows the intact vimentin substrate after incubation in the absence of protease and RNA.

Figure 7 shows the results of a titration of HIV protease activity by RNA oligonucleotide (xii). These reactions were the same as described above except that the HIV protease concentration was 10 nM and the reactions were incubated for 3 hours. Figure 7 shows that the inhibition of protease is dependent on the concentration of oligonucleotide inhibitor present during the incubation. For this particular oligonucleotide, a concentration of 30 nM causes a very significant reduction in proteolytic activity.

Example 4

Screening for HIV Protease Inhibitors

The discovery that HIV protease binds to specific nucleic acids indicates that it may be therapeutically beneficial to block this activity in vivo. The oligonucleotides of the instant invention can be used to block this HIV protease activity. These oligonucleotides can also be used to assay for other compounds that block this interaction. Compounds that block the interaction of HIV protease with nucleic acids may represent leads for anti-HIV drug development. Assays to test compounds assess their capacity to block the interactions of HIV protease with nucleic acid.

For example, 100 nM HIV-1 protease is incubated with RNA oligonucleotide (xii) under conditions as described in Example 1. The oligonucleotide is radioactively labeled so that upon filtering the reaction mixture through nitrocellulose, approximately 10,000 cpm of radioactive RNA is bound to the nitrocellulose via its interaction with HIV protease. Each compound is screened for the ability to disrupt the protease-RNA interaction by addition of 1 micromolar compound in a separate reaction. So that in

order to test 100 compounds, 100 separate reactions would be required. Alternatively, pools of compounds might be tested in a single reaction. After filtering each reaction and scintillation counting the bound RNA, the compounds that result in the lowest retention of RNA are chosen for further study as potential inhibitors of the protease-RNA interaction.

Alternative strategies for testing compounds that are well known in the art might also be applied to the reaction of HIV protease and nucleic acid.

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Beutel, Bruce A.
Coppola, George R.
Sherman, Michael I.

(ii) TITLE OF INVENTION: Oligonucleotides Which Inhibit HIV Protease Function

(iii) NUMBER OF SEQUENCES: 60

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein

(B) STREET: 6 Becker Farm Road

(C) CITY: Roseland

(D) STATE: New Jersey

(E) COUNTRY: USA

(F) ZIP: 07068

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: 3.5 inch diskette

(B) COMPUTER: IBM PS/2

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(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Olstein, Elliott M.

(B) REGISTRATION NUMBER: 24,025

(C) REFERENCE/DOCKET NUMBER: 23550-89

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 201-994-1700

(B) TELEFAX: 201-994-1744

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GGAAAGUGGA C 11

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: N is modified or unmodified adenine, cytosine, guanine, or uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

AANGU 5

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: N is modified or unmodified adenine, cytosine, guanine, or uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ANUGGA 6

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: R is a modified or unmodified purine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGAAAGUGGA CRRR - 14

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: R is a modified or unmodified purine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

RGUGAGUGUG GGCR 14

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: R is a modified or unmodified purine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

RGUGAGUGUG GGGCR 15

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

AGUGUG 6

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: Y is a modified or unmodified pyrimidine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

UNGAUNY 7

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CCUC 4

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: N is modified adenine, cytosine, guanine, or uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GGUGNA 6

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGGAGAAGUA GUGUAGGAAU UCCUCACUAG UGGAUCUUAC AUUGGAUUAU AAGGCCUGGG60

UUGUGGCUAC CAAGUGUUCA GGCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GGGAGAAGUA GUGUAGGAAU UCAAGAAGGU AUACCUCACU UUCAUCAUCG CACCUGUGAG60

CGGUGUCUUA AUUGUCGUAG GCUCGAGAGG UCACAGU97

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GGGAGAAGUA GUGUAGGAAU UCAGCCUAUA AGGUCGCCUA GAUUCUUGUU CCUGCUGUCC60

UGAGUUGGAA AGUGGACGUA GCCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GGGAGAAGUA GUGUAGGAAU UCCGAGGGAA AGUGGACGGG UCAGGCGCUU ACAAUGUUAC60

UUUCUUCUAC UAAGGUUUUG CCCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	97 bases
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear
(ii) MOLECULE TYPE:	oligonucleotide
(ix) FEATURE:	
(D) OTHER INFORMATION:	N is modified or unmodified adenine, cytosine, guanine, or uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GGGAGAAGUA GUGUAGGAAU UCUAGCGGAA AGUGGACAAA GUUGAGAAUG GAGCUCCCAU60

GCAGAUUAAU CGCCCNUUGG UCUCGAGAGG UCACAGU97

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	98 bases
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear
(ii) MOLECULE TYPE:	oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GGGAGAAGUA GUGUAGGAAU UCUGCAGGUC UGAACGCAGA GUAGAAAUGG UGUUGGUAGU60

GAAUAAAGAA GUGUGUGCUG GCCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGGAGAAGUA GUGUAGGAAU UCGUUAGUUA AAGUUAGUUU GGUGUAGUGU AUUGGAAGUC60

GAUUUGAAUG CUAGCUGUGG ACUCGAGAGG UCACAGU97

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GGGAGAAGUA GUGUAGGAAU UCACUGGAGG GUUGCUAUAA UCGGGUGAGU GUGGGCACGA60

UUAUAGUAAG ACGCGAGGGC UGCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GGGAGAAGUA GUGUAGGAAU UCAUCUGUUC CGUGCACGGA GUCAUAACAA ACUCACCUGU60

CUCGAGUGGA AAGUGGACGC AGCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GGGAGAAGUA GUGUAGGAAU UCAAUAAGUU GGGAAAGUGG ACGAACGGCU GGAGAUGGCU60

UACUCACUUC UUUCGUGCUU GCCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GGGAGAAGUA GUGUAGGAAU UCUGCUAAUU UCAAGUCAGU UGCGCGGGAA AGUGGACGAA60

CGUUGCAAUG UUGAUCCGGU GGCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 95 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GGGAGAAGUA GUGUAGGAAU UCAGGCAGUG GGGAAGUGAG UGUGGGGCGU CUCUACUUAG60

UGUGCGAUCA AGCGUACGGC UCGAGAGGUC ACAGU95

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 96 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GGGAGAAGUA GUGUAGGAAU UCAAAGCCUC AACGCUAGGU UGCGUUUAGG GAGCCAAGUA60

GUGAGUGUGG GCGACUAGGG CUCGAGAGGU CACAGU96

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GGGAGAAGUA GUGUAGGAAU UCGCACACGC AAUGCCAAAG UAGGGAUGUU GCGUCACGGU60

CUUGGGGAGU GAGAGUGGGC GCCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GGGAGAAGUA GUGUAGGAAU UCAACUUUAC UAUUAAACCG CGACGCCUUU UCAGGAUAAC60

AAAUGAAUUG GCGGCCCUCU AGCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GGGAGAAGUA GUGUAGGAAU UCCUGAAGUU GGUUUGUUGU UUGUUUUGAU AUAUCCAUAG60

AGAUAUCAGU UUGAGGUUGG UCUCGAGAGG UCACAGU97

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GGGAGAAGUA GUGUAGGAAU UCUACGUGGA UAGGUAGAUG GAGAGAUGAU AGUGGUGUAA60

CGUUUGAGAU UAAGGGUGCG ACUCGAGAGG UCACAGU97

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGGAGAAGUA GUGUAGGAAU UCCCGUCCUC UUCCGGAGGU UUGCUUAGAG GCAUAGCUAU60

CAAAUCGAUA CUUAUGGCGC ACCUCGAGAG GUCACAGU98

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 96 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGGAGAAGUA GUGUAGGAAU UCUAAGUCCG GUCUAUCGCC UCCUGUACAU GGAUCCCAAG60

GUGAAUACUC GCUUGAUGUC CUCGAGAGGU CACAGU96

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GGAAAGTGGA C 11

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(D) OTHER INFORMATION: N is modified or unmodified adenine, cytosine, guanine, thymine, or uracil

(ix) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

AANGT 5

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: N is modified or unmodified adenine, cytosine, guanine, thymine, or uracil

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:32:

ANTGGA 6

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: R is a modified or unmodified purine.

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:33:

GGAAAGTGGA CRRR 14

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) FEATURE:

(D) OTHER INFORMATION: R is a modified or unmodified purine.

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:34:

RGTGAGTGTG GGCR 14

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: R is a modified or unmodified purine.

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:35:

RGTGAGTGTG GGGCR 15

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:36:

AGTGTG 6

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: N is modified or unmodified adenine, cytosine, guanine, thymine, or uracil; Y is a modified or unmodified pyrimidine.

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:37:

TNGATNY 7

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:38:

CCTC 4

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: N is a modified or unmodified adenine, cytosine, guanine, thymine, or uracil.

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:39:

GGTGNA 6

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:40:

GGGAGAAGTA GTGTAGGAAT TCCTCACTAG TGGATCTTAC AATGGATTAT AAGGCCTGGG60

TTGTGGCTAC CAAGTGTTCA GGCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:41:

GGGAGAAGTA GTGTAGGAAT TCAAGAAGGT ATACCTCACT TTCATCATCG CACCTGTGAG60

CGGTGTCTTA ATTGTCGTAG GCTCGAGAGG TCACAGT97

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:42:

GGGAGAAGTA GTGTAGGAAT TCAGCCTATA AGGTCGCCTA GATTCTTGTT CCTGCTGTCT60

TGAGTTGGAA AGTGGACGTA GCCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:43:

GGGAGAAGTA GTGTAGGAAT TCTGAGGGAA AGTGGACGGG TCAGGCGCTT ACAATGTTAC60

TTTCTTCTAC TAAGGTTTTG CCCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(ix) FEATURE:

(D) OTHER INFORMATION: N is a modified or unmodified adenine, cytosine, guanine, thymine, or uracil.

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:44:

GGGAGAAGTA GTGTAGGAAT TCTAGCGGAA AGTGGACAAA GTTGAGAATG GAGCTCCCAT60

GCAGATTAAT CGCGCNTTGG TCTCAGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:45:

GGGAGAAGTA GTGTAGGAAT TCTGCAGGTC TGAACGCAGA GTAGAAATGG TGTTGGTAGT60

GAATAAAGAA GTGTGTGCTG GCCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:46:

GGGAGAAGTA GTGTAGGAAT TCGTTAGTTA AAGTTAGTTT GGTGTAGTGT ATTGGAAGTC60

GATTTGAATG CTAGCTGTGG ACTCGAGAGG TCACAGT97

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:47:

GGGAGAAGTA GTGTAGGAAT TCACTGGAGG GTTGCTATAA TCGGGTGAGT GTGGGCACGA60

TTATAGTAAG ACGCGAGGGC TGCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:48:

GGGAGAAGTA GTGTAGGAAT TCATCTGTTC CGTGCACGGA GTCATAACAA ACTCACCTGT60

CTCGAGTGGA AAGTGGACGC AGCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:49:

GGGAGAAGTA GTGTAGGAAT TCAATAAGTT GGGAAAGTGG ACGAACGGCT GGAGATGGCT60

TACTCACTTC TTTCGTGCTT GCCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:50:

GGGAGAAGTA GTGTAGGAAT TCTGCTAATT TCAAGTCAGT TGCGCGGGAA AGTGGACGAA60

CGTTGCAATG TTGATCCGGT GGCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 95 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:51:

GGGAGAAGTA GTGTAGGAAT TCAGGCAGTG GGGAAGTGAG TGTGGGGCGT CTCTACTTAG60

TGTGCGATCA AGCGTACGGC TCGAGAGGTC ACAGT95

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 96 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:52:

GGGAGAAGTA GTGTAGGAAT TCAAAGCCTC AACGCTAGGT TGCGTTTAGG GAGCCAAGTA60

GTGAGTGTGG GCGACTAGGC CTCGAGAGGT CACAGT96

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:53:

GGGAGAAGTA GTGTAGGAAT TCGCACACGC AATGCCAAAG TAGGGATGTT GCGTCACGGT60

CTTGGGGAGT GAGAGTGGGC GCCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:54:

GGGAGAAGTA GTGTAGGAAT TCAACTTTAC TATTAAACCG CGACGCCTTT TCAGGATAAC60

AAATGAATTG GCGGCCCTCT AGCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:55:

CGGACAAGTA GTGTAGGAAT TCCTGAAGTT GGTTTGTTGT TTGTTTTGAT ATATCCATAG60

AGATATCAGT TTGAGGTTGG TCTCGAGAGG TCACAGT97

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:56:

GGGAGAAGTA GTGTAGGAAT TCTACGTGGA TAGGTAGATG GAGAGATGAT AGTGGTGTAA60

CGTTTGAGAT TAAGGGTGCG ACTCGAGAGG TCACAGT97

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 98 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:57:

GGGAGAAGTA GTGTAGGAAT TCCCGTCCTC TTCCGGAGGT TTGCTTAGAG GCATAGCTAT60

CAAATCGATA CTTATGGCGC ACCTCGAGAG GTCACAGT98

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 96 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:58:

GGGAGAAGTA GTGTAGGAAT TCTAAGTCCG GTCTATCGCC TCCTGTACAT GGATCCCAAG60

GTGAATACTC GCTTGATGTC CTCGAGAGGT CACAGT96

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:59:

GGGAGAAGUA GUGUAGGAAU UC 22

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 bases

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: oligonucleotide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:60:

CUCGAGAGGU CACAGU 16

WHAT IS CLAIMED IS:

1. A method of inhibiting HIV protease function, comprising:

contacting HIV protease with an effective amount of an oligonucleotide which inhibits HIV protease function.

2. The method of Claim 1 wherein said oligonucleotide is a DNA oligonucleotide.

3. The method of Claim 1 wherein said oligonucleotide is an RNA oligonucleotide.

4. The method of Claim 3 wherein said RNA oligonucleotide includes at least one of the following oligonucleotide sequences:

(a) 5′ - GGAAAGUGGAC - 3′;
(b) 5′ - AANGU - 3′;
(c) 5′ - ANUGGA - 3′,
(d) 5′ - GGAAAGUGGACRRR - 3′;
(e) 5′ - RGUGAGUGUGGGCR - 3′;
(f) 5′ - RGUGAGUGUGGGGCR - 3′;
(g) 5′ - AGUGUG - 3′;
(h) 5′ - UNGAUNY - 3′;
(i) 5′ - CCUC - 3′; and
(j) 5′ - GGUGNA - 3′, wherein

A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, U is modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, or uracil.

5. The method of Claim 4 wherein said oligonucleotide has a sequence selected from the group consisting of:

(i) 5′-
GGGAGAAGUAGUGUAGGAAUUCCUCACUAGUGGAUCUUACAUUGGAUUAUAAGGCC-
UGGGUUGUGGCUACCAAGUGUUCAGGCUCGAGAGGUCACAGU-3′;

(ii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAAGAAGGUAUACCUCACUUUCAUCAUCGCACCUG-
UGAGCGGUGUCUUAAUUGUCGUAGGCUCGAGAGGUCACAGU-3';
(iii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAGCCUAUAAGGUCGCCUAGAUUCUUGUUCCUGCU-
GUCUUGAGUUGGAAAGUGGACGUAGCCUCGAGAGGUCACAGU-3';
(iv) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGAGGGAAAGUGGACGGGUCAGGCGCUUACAAUG-
UUACUUUCUUCUACUAAGGUUUUGCCCUCGAGAGGUCACAGU-3';
(v) 5'-
GGGAGAAGUAGUGUAGGAAUUCUAGCGGAAAGUGGACAAAGUUGAGAAUGGAGCUC-
CCAUGCAGAUUAAUCGCGCNUUGGUCUCGAGAGGUCACAGU-3';
(vi) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGCAGGUCUGAACGCAGAGUAGAAAUGGUGUUGG-
UAGUGAAUAAAGAAGUGUGUGCUGGCCUCGAGAGGUCACAGU-3';
(vii) 5'-
GGGAGAAGUAGUGUAGGAAUUCGUUAGUUAAAGUUAGUUUGGUGUAGUGUAUUGGA-
AGUCGAUUUGAAUGCUAGCUGUGGACUCGAGAGGUCACAGU-3';
(viii) 5'-
GGGAGAAGUAGUGUAGGAAUUCACUGGAGGGUUGCUAUAAUCGGGUGAGUGUGGGC-
ACGAUUAUAGUAAGACGCGAGGGCUGCUCGAGAGGUCACAGU-3';
(ix)
5'-
GGGAGAAGUAGUGUAGGAAUUCAUCUGUUCCGUGCACGGAGUCAUAACAAACUCAC-
CUGUCUCGAGUGGAAAGUGGACGCAGCUCGAGAGGUCACAGU-3';
(x)
5'-
GGGAGAAGUAGUGUAGGAAUUCAAUAAGUUGGGAAAGUGGACGAACGGCUGGAGAU-
GGCUUACUCACUUCUUUCGUGCUUGCCUCGAGAGGUCACAGU-3';
(xi)
5'-
GGGAGAAGUAGUGUAGGAAUUCUGCUAAUUUCAAGUCAGUUGCGCGGGAAAGUGGA-
CGAACGUUGCAAUGUUGAUCCGGUGGCUCGAGAGGUCACAGU-3;
(xii)

5'-
GGGAGAAGUAGUGUAGGAAUUCAGGCAGUGGGGAAGUGAGUGUGGGGCGUCUCUAC-
UUAGUGUGCGAUCAAGCGUACGGCUCGAGAGGUCACAGU-3';
(xiii)

5'-
GGGAGAAGUAGUGUAGGAAUUCAAAGCCUCAACGCUAGGUUGCGUUUAGGGAGCC-
AAGUAGUGAGUGUGGGCGACUAGGGCUCGAGAGGUCACAGU-3';
(xiv)
5'-
GGGAGAAGUAGUGUAGGAAUUCGCACACGCAAUGCCAAAGUAGGGAUGUUGCGUCA-
CGGUCUUGGGGAGUGAGAGUGGGCGCCUCGAGAGGUCACAGU-3';
(xv)
5'-
GGGAGAAGUAGUGUAGGAAUUCAACUUUACUAUUAAACCGCGACGCCUUUUCAGGA-
UAACAAAUGAAUUGGCGGCCCUCUAGCUCGAGAGGUCACAGU-3';
(xvi)
5'-
GGGAGAAGUAGUGUAGGAAUUCCUGAAGUUGGUUUGUUGUUUGUUUUGAUAUAUCC-
AUAGAGAUAUCAGUUUGAGGUUGGUCUCGAGAGGUCACAGU-3';
(xvii)
5'-
GGGAGAAGUAGUGUAGGAAUUCUACGUGGAUAGGUAGAUGGAGAGAUGAUAGUGGU-
GUAACGUUUGAGAUUAAGGGUGCGACUCGAGAGGUCACAGU-3';
(xviii)
5'-
GGGAGAAGUAGUGUAGGAAUUCCCGUCCUCUUCCGGAGGUUUGCUUAGAGGCAUAG-
CUAUCAAAUCGAUACUUAUGGCGCACCUCGAGAGGUCACAGU-3'; and
(xix)
5'-
GGGAGAAGUAGUGUAGGAAUUCUAAGUCCGGUCUAUCGCCUCCUGUACAUGGAUCC-
CAAGGUGAAUACUCGCUUGAUGUCCUCGAGAGGUCACAGU-3'.

6. The method of Claim 1 wherein said oligonucleotide has from about 5 to about 100 nucleotide units.

7. The method of Claim 6 wherein said oligonucleotide has from about 8 to about 60 nucleotide units.

8. The method of Claim 1 wherein said oligonucleotide has no greater than 25% of its bases which are cytosine residues.

The 9. method of Claim 8 wherein said oligonucleotide has no greater than 20% of its bases which are cytosine residues.

10. The method of Claim 9 wherein said oligonucleotide has no greater than 15% of its bases which are cytosine residues.

11. The method of Claim 4 wherein said oligonucleotide includes a looped region bounded by a based-paired stem region, and wherein at least part of said at least one of sequences (a) through (j) of said oligonucleotide is contained within said looped region.

12. The method of Claim 2 wherein said DNA oligonucleotide includes at least one of the following sequences:

(k) 5'-GGAAAGTGGAC-3';
(l) 5'-AANGT-3';
(m) 5'-ANTGGA-3';
(n) 5'-GGAAAGTGGACRRR-3';
(o) 5'-RGTGAGTGTGGGCR-3';
(p) 5'-RGTGAGTGTGGGGCR-3';
(q) 5'-AGTGTG-3';
(r) 5'-TNGATNY-3';
(s) 5'-CCTC-3'; and
(t) 5'-GGTGNA-3',

wherein A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, T is modified or unmodified thymine or modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, thymine, or uracil.

13. The method of Claim 12 wherein said oligonucleotide has a sequence selected from the group consisting of:

(xx) 5'-
GGGAGAAGTAGTGTAGGAATTCCTCACTAGTGGATCTTACATTGGATTATAAGGCC-
TGGGTTGTGGCTACCAAGTGTTCAGGCTCGAGAGGTCACAGT-3';

(xxi) 5'-
GGGAGAAGTAGTGTAGGAATTCAAGAAGGTATACCTCACTTTCATCATCGCACCTG-
TGAGCGGTGTCTTAATTGTCGTAGGCTCGAGAGGTCACAGT-3';

(xxii) 5'-
GGGAGAAGTAGTGTAGGAATTCAGCCTATAAGGTCGCCTAGATTCTTGTTCCTGCT-
GTCTTGAGTTGGAAAGTGGACGTAGCCTCGAGAGGTCACAGT-3';

(xxiii) 5'-
GGGAGAAGTAGTGTAGGAATTCTGAGGGAAAGTGGACGGGTCAGGCGCTTACAATG-
TTACTTTCTTCTACTAAGGTTTTGCCCTCGAGAGGTCACAGT-3';

(xxiv) 5'-
GGGAGAAGTAGTGTAGGAATTCTAGCGGAAAGTGGACAAAGTTGAGAATGGAGCTC-
CCATGCAGATTAATCGCGCNTTGGTCTCGAGAGGTCACAGT-3';

(xxv) 5'-
GGGAGAAGTAGTGTAGGAATTCTGCAGGTCTGAACGCAGAGTAGAAATGGTGTTGG-
TAGTGAATAAAGAAGTGTGTGCTGGCCTCGAGAGGTCACAGT-3';

(xxvi) 5'-
GGGAGAAGTAGTGTAGGAATTCGTTAGTTAAAGTTAGTTTGGTGTAGTGTATTGGA-
AGTCGATTTGAATGCTAGCTGTGGACTCGAGAGGTCACAGT-3';

(xxvii) 5'-
GGGAGAAGTAGTGTAGGAATTCACTGGAGGGTTGCTATAATCGGGTGAGTGTGGGC-
ACGATTATAGTAAGACGCGAGGGCTGCTCGAGAGGTCACAGT-3';

(xxviii)
5'-GGGAGAAGTAGTGTAGGAATTCATCTGTTCCGTGCACGGAGTCATAACAAACTC-
ACCTGTCTCGAGTGGAAAGTGGACGCAGCTCGAGAGGTCACAGT-3';

(xxix)
5'-
GGGAGAAGTAGTGTAGGAATTCAATAAGTTGGGAAAGTGGACGAACGGCTGGAGAT-
GGCTTACTCACTTCTTTCGTGCTTGCCTCGAGAGGTCACAGT-3';

(xxx)

5'-
GGGAGAAGTAGTGTAGGAATTCTGCTAATTTCAAGTCAGTTGCGCGGGAAAGTGGA-
CGAACGTTGCAATGTTGATCCGGTGGCTCGAGAGGTCACAGT-3';
(xxxi)
5'-
GGGAGAAGTAGTGTAGGAATTCAGGCAGTGGGGAAGTGAGTGTGGGGCGTCTCTAC-
TTAGTGTGCGATCAAGCGTACGGCTCGAGAGGTCACAGT-3';
(xxxii)
5'-GGGAGAAGTAGTGTAGGAATTCAAAGCCTCAACGCTAGGTTGCGTTTAGGGAGCC-
AAGTAGTGAGTGTGGGCGACTAGGGCTCGAGAGGTCACAGT-3';
(xxxiii)
5'-
GGGAGAAGTAGTGTAGGAATTCGCACACGCAATGCCAAAGTAGGGATGTTGCGTCA-
CGGTCTTGGGGAGTGAGAGTGGGCGCCTCGAGAGGTCACAGT-3';
(xxxiv)
5'-
GGGAGAAGTAGTGTAGGAATTCAACTTTACTATTAAACCGCGACGCCTTTTCAGGA-
TAACAAATGAATTGGCGGCCCTCTAGCTCGAGAGGTCACAGT-3';
(xxxv)
5'-
GGGAGAAGTAGTGTAGGAATTCCTGAAGTTGGTTTGTTGTTTGTTTTGATATATCC-
ATAGAGATATCAGTTTGAGGTTGGTCTCGAGAGGTCACAGT-3';
(xxxvi)
5'-
GGGAGAAGTAGTGTAGGAATTCTACGTGGATAGGTAGATGGAGAGATGATAGTGGT-
GTAACGTTTGAGATTAAGGGTGCGACTCGAGAGGTCACAGT-3';
(xxxvii)
5'-
GGGAGAAGTAGTGTAGGAATTCCCGTCCTCTTCCGGAGGTTTGCTTAGAGGCATAG-
CTATCAAATCGATACTTATGGCGCACCTCGAGAGGTCACAGT-3'; and
(xxxviii)
5'-
GGGAGAAGTAGTGTAGGAATTCTAAGTCCGGTCTATCGCCTCCTGTACATGGATCC-
CAAGGTGAATACTCGCTTGATGTCCTCGAGAGGTCACAGT-3'.

14. An oligonucleotide which inhibits HIV protease function, said oligonucleotide including at least one of the following oligonucleotide sequences:

(a) 5′ - GGAAAGUGGAC - 3′;

(b) 5′ - AANGU - 3′;

(c) 5′ - ANUGGA - 3′;

(d) 5′ - GGAAAGUGGACRRR - 3′;

(e) 5′ - RGUGAGUGUGGGCR - 3′;

(f) 5′ - RGUGAGUGUGGGGCR - 3′;

(g) 5′ - AGUGUG - 3′;

(h) 5′ - UNGAUNY - 3′;

(i) 5′ - CCUC - 3′; and

(j) 5′ - GGUGNA - 3′, wherein

A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, U is modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, or uracil.

15. The oligonucleotide of Claim 14 wherein said oligonucleotide is selected from the group consisting of:

(i)
5′-
GGGAGAAGUAGUGUAGGAAUUCCUCACUAGUGGAUCUUACAUUGGAUUAUAAGGCC-
UGGGUUGUGGCUACCAAGUGUUCAGGCUCGAGAGGUCACAGU-3′;

(ii)
5′-
GGGAGAAGUAGUGUAGGAAUUCAAGAAGGUAUACCUCACUUUCAUCAUCGCACCUG-
UGAGCGGUGUCUUAAUUGUCGUAGGCUCGAGAGGUCACAGU-3′;

(iii) 5′-
GGGAGAAGUAGUGUAGGAAUUCAGCCUAUAAGGUCGCCUAGAUUCUUGUUCCUGCU-
GUCUUGAGUUGGAAAGUGGACGUAGCCUCGAGAGGUCACAGU-3′;

(iv) 5′-
GGGAGAAGUAGUGUAGGAAUUCUGAGGGAAAGUGGACGGGUCAGGCGCUUACAAUG-
UUACUUUCUUCUACUAAGGUUUUGCCCUCGAGAGGUCACAGU-3′;

(v) 5'-
GGGAGAAGUAGUGUAGGAAUUCUAGCGGAAAGUGGACAAAGUUGAGAAUGGAGCUC-
CCAUGCAGAUUAAUCGCGCNUUGGUCUCGAGAGGUCACAGU-3';
(vi) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGCAGGUCUGAACGCAGAGUAGAAAUGGUGUUGG-
UAGUGAAUAAAGAAGUGUGUGCUGGCCUCGAGAGGUCACAGU-3';
(vii) 5'-
GGGAGAAGUAGUGUAGGAAUUCGUUAGUUAAAGUUAGUUUGGUGUAGUGUAUUGGA-
AGUCGAUUUGAAUGCUAGCUGUGGACUCGAGAGGUCACAGU-3';
(viii) 5'-
GGGAGAAGUAGUGUAGGAAUUCACUGGAGGGUUGCUAUAAUCGGGUGAGUGUGGGC-
ACGAUUAUAGUAAGACGCGAGGGCUGCUCGAGAGGUCACAGU-3';
(ix)
5'-
GGGAGAAGUAGUGUAGGAAUUCAUCUGUUCCGUGCACGGAGUCAUAACAAACUCAC-
CUGUCUCGAGUGGAAAGUGGACGCAGCUCGAGAGGUCACAGU-3';
(x)
5'-
GGGAGAAGUAGUGUAGGAAUUCAAUAAGUUGGGAAAGUGGACGAACGGCUGGAGAU-
GGCUUACUCACUUCUUUCGUGCUUGCCUCGAGAGGUCACAGU-3';
(xi)
5'-
GGGAGAAGUAGUGUAGGAAUUCUGCUAAUUUCAAGUCAGUUGCGCGGGAAAGUGGA-
CGAACGUUGCAAUGUUGAUCCGGUGGCUCGAGAGGUCACAGU-3;
(xii)
5'-
GGGAGAAGUAGUGUAGGAAUUCAGGCAGUGGGGAAGUGAGUGUGGGGCGUCUCUAC-
UUAGUGUGCGAUCAAGCGUACGGCUCGAGAGGUCACAGU-3';
(xiii)
5'-GGGAGAAGUAGUGUAGGAAUUCAAAGCCUCAACGCUAGGUUGCGUUUAGGGAGCC-
AAGUAGUGAGUGUGGGCGACUAGGGCUCGAGAGGUCACAGU-3';
(xiv)
5'-
GGGAGAAGUAGUGUAGGAAUUCGCACACGCAAUGCCAAAGUAGGGAUGUUGCGUCA-
CGGUCUUGGGGAGUGAGAGUGGGCGCCUCGAGAGGUCACAGU-3';

(xv)
5'-
GGGAGAAGUAGUGUAGGAAUUCAACUUUACUAUUAAACCGCGACGCCUUUUCAGGA-
UAACAAAUGAAUUGGCGGCCCUCUAGCUCGAGAGGUCACAGU-3';
(xvi)
5'-
GGGAGAAGUAGUGUAGGAAUUCCUGAAGUUGGUUUGUUGUUUGUUUUGAUAUAUCC-
AUAGAGAUAUCAGUUUGAGGUUGGUCUCGAGAGGUCACAGU-3';
(xvii)
5'-
GGGAGAAGUAGUGUAGGAAUUCUACGUGGAUAGGUAGAUGGAGAGAUGAUAGUGGU-
GUAACGUUUGAGAUUAAGGGUGCGACUCGAGAGGUCACAGU-3';
(xviii)
5'-
GGGAGAAGUAGUGUAGGAAUUCCCGUCCUCUUCCGGAGGUUUGCUUAGAGGCAUAG-
CUAUCAAAUCGAUACUUAUGGCGCACCUCGAGAGGUCACAGU-3'; and
(xix)
5'-
GGGAGAAGUAGUGUAGGAAUUCUAAGUCCGGUCUAUCGCCUCCUGUACAUGGAUCC-
CAAGGUGAAUACUCGCUUGAUGUCCUCGAGAGGUCACAGU-3'.

16. The oligonucleotide of Claim 14 wherein said oligonucleotide has from about 5 about to about 100 nucleotide units.

17. The oligonucleotide of Claim 16 wherein said oligonucleotide has from about 8 to about 60 nucleotide units.

18. The oligonucleotide of Claim 14 wherein said oligonucleotide has no greater than 25% of its bases which are cytosine residues.

19. The oligonucleotide of Claim 18 wherein said oligonucleotide has no greater than 20% of its bases which are cytosine residues.

20. The oligonucleotide of Claim 19 wherein said oligonucleotide has no greater than 15% of its bases which are cytosine residues.

21. The oligonucleotide of Claim 14 wherein said oligonucleotide includes a looped region bounded by a base-paired stem region, and wherein at least a portion of said at least one of sequences (a) through (j) of said oligonucleotide is contained within said looped region.

22. An oligonucleotide which inhibits HIV protease function, said oligonucleotide including at least one of the following oligonucleotide sequences:

(k) 5'-GGAAAGTGGAC-3';

(l) 5'-AANGT-3';

(m) 5'-ANTGGA-3';

(n) 5'-GGAAAGTGGACRRR-3';

(o) 5'-RGTGAGTGTGGGCR-3';

(p) 5'-RGTGAGTGTGGGGCR-3';

(q) 5'-AGTGTG-3';

(r) 5'-TNGATNY-3';

(s) 5'-CCTC-3'; and

(t) 5'-GGTGNA-3', wherein

A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, T is modified or unmodified thymine or modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, thymine, or uracil.

23. The oligonucleotide of Claim 22 wherein said oligonucleotide is selected from the group consisting of:

(xx) 5'-
GGGAGAAGTAGTGTAGGAATTCCTCACTAGTGGATCTTACATTGGATTATAAGGCC-
TGGGTTGTGGCTACCAAGTGTTCAGGCTCGAGAGGTCACAGT-3';

(xxi) 5'-
GGGAGAAGTAGTGTAGGAATTCAAGAAGGTATACCTCACTTTCATCATCGCACCTG-
TGAGCGGTGTCTTAATTGTCGTAGGCTCGAGAGGTCACAGT-3';

(xxii) 5'-
GGGAGAAGTAGTGTAGGAATTCAGCCTATAAGGTCGCCTAGATTCTTGTTCCTGCT-
GTCTTGAGTTGGAAAGTGGACGTAGCCTCGAGAGGTCACAGT-3';

(xxiii) 5'-
GGGAGAAGTAGTGTAGGAATTCTGAGGGAAAGTGGACGGGTCAGGCGCTTACAATG-
TTACTTTCTTCTACTAAGGTTTTGCCCTCGAGAGGTCACAGT-3';
(xxiv) 5'-
GGGAGAAGTAGTGTAGGAATTCTAGCGGAAAGTGGACAAAGTTGAGAATGGAGCTC-
CCATGCAGATTAATCGCGCNTTGGTCTCGAGAGGTCACAGT-3';
(xxv) 5'-
GGGAGAAGTAGTGTAGGAATTCTGCAGGTCTGAACGCAGAGTAGAAATGGTGTTGG-
TAGTGAATAAAGAAGTGTGTGCTGGCCTCGAGAGGTCACAGT-3';
(xxvi) 5'-
GGGAGAAGTAGTGTAGGAATTCGTTAGTTAAAGTTAGTTTGGTGTAGTGTATTGGA-
AGTCGATTTGAATGCTAGCTGTGGACTCGAGAGGTCACAGT-3';
(xxvii) 5'-
GGGAGAAGTAGTGTAGGAATTCACTGGAGGGTTGCTATAATCGGGTGAGTGTGGGCAC-
GATTATAGTAAGACGCGAGGGCTGCTCGAGAGGTCACAGT-3';
(xxviii)
5'-GGGAGAAGTAGTGTAGGAATTCATCTGTTCCGTGCACGGAGTCATAACAAACTC-
ACCTGTCTCGAGTGGAAAGTGGACGCAGCTCGAGAGGTCACAGT-3';
(xxix)
5'-
GGGAGAAGTAGTGTAGGAATTCAATAAGTTGGGAAAGTGGACGAACGGCTGGAGAT-
GGCTTACTCACTTCTTTCGTGCTTGCCTCGAGAGGTCACAGT-3';
(xxx)
5'-
GGGAGAAGTAGTGTAGGAATTCTGCTAATTTCAAGTCAGTTGCGCGGGAAAGTGGA-
CGAACGTTGCAATGTTGATCCGGTGGCTCGAGAGGTCACAGT-3';
(xxxi)
5'-
GGGAGAAGTAGTGTAGGAATTCAGGCAGTGGGGAAGTGAGTGTGGGGCGTCTCTAC-
TTAGTGTGCGATCAAGCGTACGGCTCGAGAGGTCACAGT-3';
(xxxii)
5'-GGGAGAAGTAGTGTAGGAATTCAAAGCCTCAACGCTAGGTTGCGTTTAGGGAGCC-
AAGTAGTGAGTGTGGGCGACTAGGGCTCGAGAGGTCACAGT-3';
(xxxiii)

5'-
GGGAGAAGTAGTGTAGGAATTCGCACACGCAATGCCAAAGTAGGGATGTTGCGTCA-
CGGTCTTGGGGAGTGAGAGTGGGCGCCTCGAGAGGTCACAGT-3';

(xxxiv)

5'-
GGGAGAAGTAGTGTAGGAATTCAACTTTACTATTAAACCGCGACGCCTTTTCAGGA-
TAACAAATGAATTGGCGGCCCTCTAGCTCGAGAGGTCACAGT-3';

(xxxv)

5'-
GGGAGAAGTAGTGTAGGAATTCCTGAAGTTGGTTTGTTGTTTGTTTTGATATATCC-
ATAGAGATATCAGTTTGAGGTTGGTCTCGAGAGGTCACAGT-3';

(xxxvi)

5'-
GGGAGAAGTAGTGTAGGAATTCTACGTGGATAGGTAGATGGAGAGATGATAGTGGT-
GTAACGTTTGAGATTAAGGGTGCGACTCGAGAGGTCACAGT-3';

(xxxvii)

5'-
GGGAGAAGTAGTGTAGGAATTCCCGTCCTCTTCCGGAGGTTTGCTTAGAGGCATAG-
CTATCAAATCGATACTTATGGCGCACCTCGAGAGGTCACAGT-3'; and

(xxxviii)

5'-
GGGAGAAGTAGTGTAGGAATTCTAAGTCCGGTCTATCGCCTCCTGTACATGGATCC-
CAAGGTGAATACTCGCTTGATGTCCTCGAGAGGTCACAGT-3'.

24. The oligonucleotide of Claim 22 wherein said oligonucleotide has from about 5 to about 100 nucleotide units.

25. The oligonucleotide of Claim 24 wherein said oligonucleotide has from about 8 to about 60 nucleotide units.

26. The oligonucleotide of Claim 22 wherein said oligonucleotide has no greater than 25% of its bases which are cytosine residues.

27. The oligonucleotide of Claim 26 wherein said oligonucleotide has no greater than 20% of its bases which are cytosine residues.

28. The oligonucleotide of Claim 27 wherein said oligonucleotide has no greater than 15% of its bases which are cytosine residues.

29. The oligonucleotide of Claim 22 wherein said oligonucleotide includes a looped region bounded by a base-paired stem region, and wherein at least a portion of said at least one of sequences (k) through (t) of said oligonucleotide is contained within said looped region.

30. A composition for inhibiting HIV protease function, comprising:

(a) an oligonucleotide, said oligonucleotide including at least one of the following oligonucleotide sequences:

(a) 5′ - GGAAAGUGGAC - 3′;
(b) 5′ - AANGU - 3′;
(c) 5′ - ANUGGA - 3′;
(d) 5′ - GGAAAGUGGACRRR-3′;
(e) 5′ - RGUGAGUGUGGGGCR-3′;
(f) 5′ - RGUGAGUGUGGGGGCR-3′;
(g) 5′ - AGUGUG-3′;
(h) 5′ - UNGAUNY-3′;
(i) 5′ - CCUC-3′; and
(j) 5′ - GGUGNA-3′, wherein

A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, U is modified or unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, or uracil; and (b) an acceptable pharmaceutical carrier, wherein said oligonucleotide is present in an amount effective to inhibit HIV protease function.

31. The composition of Claim 30 wherein said oligonucleotide has from about 5 to about 100 nucleotide units.

32. The composition of Claim 31 wherein said oligonucleotide has from about 8 to about 60 nucleotide units.

33. The composition of Claim 30 wherein said oligonucleotide is selected from the group consisting of:

(i) 5'-
GGGAGAAGUAGUGUAGGAAUUCCUCACUAGUGGAUCUUACAUUGGAUUAUAAGGC-
CUGGGUUGUGGCUACCAAGUGUUCAGGCUCGAGAGGUCACAGU-3';

(ii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAAGAAGGUAUACCUCACUUUCAUCAUCGCACCU-
GUGAGCGGUGUCUUAAUUGUCGUAGGCUCGAGAGGUCACAGU-3';

(iii) 5'-
GGGAGAAGUAGUGUAGGAAUUCAGCCUAUAAGGUCGCCUAGAUUCUUGUUCCUGC-
UGUCUUGAGUUGGAAAGUGGACGUAGCCUCGAGAGGUCACAGU-3';

(iv) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGAGGGAAAGUGGACGGGUCAGGCGCUUACAAU-
GUUACUUUCUUCUACUAAGGUUUUGCCCUCGAGAGGUCACAGU-3';

(v) 5'-
GGGAGAAGUAGUGUAGGAAUUCUAGCGGAAAGUGGACAAAGUUGAGAAUGGAGCU-
CCCAUGCAGAUUAAUCGCGCNUUGGUCUCGAGAGGUCACAGU-3';

(vi) 5'-
GGGAGAAGUAGUGUAGGAAUUCUGCAGGUCUGAACGCAGAGUAGAAAUGGUGUUG-
GUAGUGAAUAAAGAAGUGUGUGCUGGCCUCGAGAGGUCACAGU-3';

(vii) 5'-
GGGAGAAGUAGUGUAGGAAUUCGUUAGUUAAAGUUAGUUUGGUGUAGUGUAUUGG-
AAGUCGAUUUGAAUGCUAGCUGUGGACUCGAGAGGUCACAGU-3';

(viii) 5'-
GGGAGAAGUAGUGUAGGAAUUCACUGGAGGGUUGCUAUAAUCGGGUGAGUGUGGGCAC-
GAUUAUAGUAAGACGCGAGGGCUGCUCGAGAGGUCACAGU-3';

(ix)
5'-
GGGAGAAGUAGUGUAGGAAUUCAUCUGUUCCGUGCACGGAGUCAUAACAAACUCAC-
CUGUCUCGAGUGGAAAGUGGACGCAGCUCGAGAGGUCACAGU-3';

(x)

5'-
GGGAGAAGUAGUGUAGGAAUUCAAUAAGUUGGGAAAGUGGACGAACGGCUGGAGAU-
GGCUUACUCACUUCUUUCGUGCUUGCCUCGAGAGGUCACAGU-3';
(xi)
5'-
GGGAGAAGUAGUGUAGGAAUUCUGCUAAUUUCAAGUCAGUUGCGCGGGAAAGUGGA-
CGAACGUUGCAAUGUUGAUCCGGUGGCUCGAGAGGUCACAGU-3;
(xii)
5'-
GGGAGAAGUAGUGUAGGAAUUCAGGCAGUGGGGAAGUGAGUGUGGGGCGUCUCUAC-
UUAGUGUGCGAUCAAGCGUACGGCUCGAGAGGUCACAGU-3';
(xiii)
5'-GGGAGAAGUAGUGUAGGAAUUCAAAGCCUCAACGCUAGGUUGCGUUUAGGGAGCC-
AAGUAGUGAGUGUGGGCGACUAGGGCUCGAGAGGUCACAGU-3';
(xiv)
5'-
GGGAGAAGUAGUGUAGGAAUUCGCACACGCAAUGCCAAAGUAGGGAUGUUGCGUCA-
CGGUCUUGGGGAGUGAGAGUGGGCGCCUCGAGAGGUCACAGU-3';
(xv)
5'-
GGGAGAAGUAGUGUAGGAAUUCAACUUUACUAUUAAACCGCGACGCCUUUUCAGGA-
UAACAAAUGAAUUGGCGGCCCUCUAGCUCGAGAGGUCACAGU-3';
(xvi)
5'-
GGGAGAAGUAGUGUAGGAAUUCCUGAAGUUGGUUUGUUGUUUGUUUUGAUAUAUCC-
AUAGAGAUAUCAGUUUGAGGUUGGUCUCGAGAGGUCACAGU-3';
(xvii)
5'-
GGGAGAAGUAGUGUAGGAAUUCUACGUGGAUAGGUAGAUGGAGAGAUGAUAGUGGU-
GUAACGUUUGAGAUUAAGGGUGCGACUCGAGAGGUCACAGU-3';
(xviii)
5'-
GGGAGAAGUAGUGUAGGAAUUCCCGUCCUCUUCCGGAGGUUUGCUUAGAGGCAUAG-
CUAUCAAAUCGAUACUUAUGGCGCACCUCGAGAGGUCACAGU-3'; and
(xix)

5'-
GGGAGAAGUAGUGUAGGAAUUCUAAGUCCGGUCUAUCGCCUCCUGUACAUGGAUCC-
CAAGGUGAAUACUCGCUUGAUGUCCUCGAGAGGUCACAGU-3'.

34. The composition of Claim 30 wherein said oligonucleotide has no greater than 25% of its bases which are cytosine residues.

35. The composition of Claim 34 wherein said oligonucleotide has no greater than 20% of its bases which are cytosine residues.

36. The composition of Claim 35 wherein said oligonucleotide has no greater than 15% of its bases which are cytosine residues.

37. The composition of Claim 30 wherein said oligonucleotide includes a looped region bounded by a base-paired stem region, and wherein at least a portion of said at least one of sequences (a) through (j) of said oligonucleotide is contained within said looped region.

38. A composition for inhibiting HIV protease function, comprising:

(a) an oligonucleotide, said oligonucleotide including at least one of the following oligonucleotide sequences:

(k) 5'-GGAAAGTGGAC-3';
(l) 5'-AANGT-3';
(m) 5'-ANTGGA-3';
(n) 5'-GGAAAGTGGACRRR-3';
(o) 5'-RGTGAGTGTGGGCR-3';
(p) 5'-RGTGAGTGTGGGGCR-3';
(q) 5'-AGTGTG-3';
(r) 5'-TNGATNY-3';
(s) 5'-CCTC-3'; and
(t) 5'-GGTGNA-3',

wherein A is modified or unmodified adenine, C is modified or unmodified cytosine, G is modified or unmodified guanine, T is modified or unmodified thymine or modified or

unmodified uracil, R is modified or unmodified purine, Y is modified or unmodified pyrimidine, and N is modified or unmodified adenine, cytosine, guanine, thymine or uracil; and (b) an acceptable pharmaceutical carrier, wherein said oligonucleotide is present in an amount effective to inhibit HIV protease function.

39. The composition of Claim 38 wherein said oligonucleotide is selected from the group consisting of:

(xx) 5'-
GGGAGAAGTAGTGTAGGAATTCCTCACTAGTGGATCTTACATTGGATTATAAGGCC-
TGGGTTGTGGCTACCAAGTGTTCAGGCTCGAGAGGTCACAGT-3';

(xxi) 5'-
GGGAGAAGTAGTGTAGGAATTCAAGAAGGTATACCTCACTTTCATCATCGCACCTG-
TGAGCGGTGTCTTAATTGTCGTAGGCTCGAGAGGTCACAGT-3';

(xxii) 5'-
GGGAGAAGTAGTGTAGGAATTCAGCCTATAAGGTCGCCTAGATTCTTGTTCCTGCT-
GTCTTGAGTTGGAAAGTGGACGTAGCCTCGAGAGGTCACAGT-3';

(xxiii) 5'-
GGGAGAAGTAGTGTAGGAATTCTGAGGGAAAGTGGACGGGTCAGGCGCTTACAATG-
TTACTTTCTTCTACTAAGGTTTTGCCCTCGAGAGGTCACAGT-3';

(xxiv) 5'-
GGGAGAAGTAGTGTAGGAATTCTAGCGGAAAGTGGACAAAGTTGAGAATGGAGCTC-
CCATGCAGATTAATCGCGCNTTGGTCTCGAGAGGTCACAGT-3';

(xxv) 5'-
GGGAGAAGTAGTGTAGGAATTCTGCAGGTCTGAACGCAGAGTAGAAATGGTGTTGG-
TAGTGAATAAAGAAGTGTGTGCTGGCCTCGAGAGGTCACAGT-3';

(xxvi) 5'-
GGGAGAAGTAGTGTAGGAATTCGTTAGTTAAAGTTAGTTTGGTGTAGTGTATTGGA-
AGTCGATTTGAATGCTAGCTGTGGACTCGAGAGGTCACAGT-3';

(xxvii) 5'-
GGGAGAAGTAGTGTAGGAATTCACTGGAGGGTTGCTATAATCGGGTGAGTGTGGGC-
ACGATTATAGTAAGACGCGAGGGCTGCTCGAGAGGTCACAGT-3';

(xxviii)
5'-GGGAGAAGTAGTGTAGGAATTCATCTGTTCCGTGCACGGAGTCATAACAAACTC-
ACCTGTCTCGAGTGGAAAGTGGACGCAGCTCGAGAGGTCACAGT-3';

(xxix)
5'-
GGGAGAAGTAGTGTAGGAATTCAATAAGTTGGGAAAGTGGACGAACGGCTGGAGAT-
GGCTTACTCACTTCTTTCGTGCTTGCCTCGAGAGGTCACAGT-3';
(xxx)
5'-
GGGAGAAGTAGTGTAGGAATTCTGCTAATTTCAAGTCAGTTGCGCGGGAAAGTGGA-
CGAACGTTGCAATGTTGATCCGGTGGCTCGAGAGGTCACAGT-3';
(xxxi)
5'-
GGGAGAAGTAGTGTAGGAATTCAGGCAGTGGGGAAGTGAGTGTGGGGCGTCTCTAC-
TTAGTGTGCGATCAAGCGTACGGCTCGAGAGGTCACAGT-3';
(xxxii)
5'-GGGAGAAGTAGTGTAGGAATTCAAAGCCTCAACGCTAGGTTGCGTTTAGGGAGCC-
AAGTAGTGAGTGTGGGCGACTAGGGCTCGAGAGGTCACAGT-3';
(xxxiii)
5'-
GGGAGAAGTAGTGTAGGAATTCGCACACGCAATGCCAAAGTAGGGATGTTGCGTCA-
CGGTCTTGGGGAGTGAGAGTGGGCGCCTCGAGAGGTCACAGT-3';
(xxxiv)
5'-
GGGAGAAGTAGTGTAGGAATTCAACTTTACTATTAAACCGCGACGCCTTTTCAGGA-
TAACAAATGAATTGGCGGCCCTCTAGCTCGAGAGGTCACAGT-3';
(xxxv)
5'-
GGGAGAAGTAGTGTAGGAATTCCTGAAGTTGGTTTGTTGTTTGTTTTGATATATCC-
ATAGAGATATCAGTTTGAGGTTGGTCTCGAGAGGTCACAGT-3';
(xxxvi)
5'-
GGGAGAAGTAGTGTAGGAATTCTACGTGGATAGGTAGATGGAGAGATGATAGTGGT-
GTAACGTTTGAGATTAAGGGTGCGACTCGAGAGGTCACAGT-3';
(xxxvii)
5'-
GGGAGAAGTAGTGTAGGAATTCCCGTCCTCTTCCGGAGGTTTGCTTAGAGGCATAG-
CTATCAAATCGATACTTATGGCGCACCTCGAGAGGTCACAGT-3'; and

(xxxviii)
5'-
GGGAGAAGTAGTGTAGGAATTCTAAGTCCGGTCTATCGCCTCCTGTACATGGATCC-
CAAGGTGAATACTCGCTTGATGTCCTCGAGAGGTCACAGT-3'.

40. The composition of Claim 38 wherein said oligonucleotide has from about 5 to about 100 nucleotide units.

41. The composition of Claim 40 wherein said oligonucleotide has from about 8 to about 60 nucleotide units.

42. The composition of Claim 38 wherein said oligonucleotide has no greater than 25% of its bases which are cytosine residues.

43. The composition of Claim 42 wherein said oligonucleotide has no greater than 20% of its bases which are cytosine residues.

44. The composition of Claim 43 wherein said oligonucleotide has no greater than 15% of its bases which are cytosine residues.

45. The composition of Claim 34 wherein said oligonucleotide includes a looped region bounded by a base-paired stem region, and wherein at least a portion of said at least one of sequences (k) through (t) of said oligonucleotide is contained within said looped region.

46. A method of treating HIV infection in a host, comprising:

administering to a host cell infected with HIV an expression vector which includes a nucleic acid sequence which (i) inhibits HIV protease function; or (ii) encodes a nucleic acid sequence which inhibits HIV protease function.

47. A method of preventing HIV infection in a host, comprising:

administering to a host cell an expression vector which includes a nucleic acid sequence which (i)

inhibits HIV protease function; or (ii) encodes a nucleic acid sequence which inhibits HIV protease function.

48. The method of Claim 1 wherein at least one nucleotide unit of said oligonucleotide is substituted with a conjugate group selected from the group consisting of:

(a) amino acids;
(b) peptides, polypeptides, and proteins;
(c) dipeptide mimics;
(d) sugars;
(e) sugar phosphates;
(f) neurotransmitters;
(g) hormones;
(h) poly (hydroxypropylmethacrylamide);
(i) polyethylene imine;
(j) dextrans;
(k) polymaleic anhydride;
(l) cyclodextrins;
(m) starches;
(n) steroids;
(o) acridine;
(p) vitamins; and
(q) polyakylene glycols.

49. The oligonucleotide of Claim 14 wherein at least one nucleotide unit of said oligonucleotide is substituted with a conjugate group selected from the group consisting of:

(a) amino acids;
(b) peptides, polypeptides, and proteins;
(c) dipeptide mimics;
(d) sugars;
(e) sugar phosphates;
(f) neurotransmitters;
(g) hormones;
(h) poly (hydroxypropylmethacrylamide);
(i) polyethylene imine;
(j) dextrans;

(k) polymaleic anhydride;
(l) cyclodextrins;
(m) starches;
(n) steroids;
(o) acridine;
(p) vitamins; and
(q) polyalkylene glycols.

50. The oligonucleotide of Claim 22, wherein at least one nucleotide unit of said oligonucleotide is substituted with a conjugate group selected from the group consisting of:

(a) amino acids;
(b) peptides, polypeptides, and proteins;
(c) dipeptide mimics;
(d) sugars;
(e) sugar phosphates;
(f) neurotransmitters;
(g) hormones;
(h) poly (hydroxypropylmethacrylamide);
(i) polyethylene imine;
(j) dextrans;
(k) polymaleic anhydride;
(l) cyclodextrins;
(m) starches;
(n) steroids;
(o) acridine;
(p) vitamins; and
(q) polyalkylene glycols.

51. The composition of Claim 30, wherein at least one nucleotide unit of said oligonucleotide is substituted with a conjugate group selected from the group consisting of:

(a) amino acids;
(b) peptides, polypeptides, and proteins;
(c) dipeptide mimics;
(d) sugars;
(e) sugar phosphates;

(f) neurotransmitters;
(g) hormones;
(h) poly (hydroxypropylmethacrylamide);
(i) polyethylene imine;
(j) dextrans;
(k) polymaleic anhydride;
(l) cyclodextrins;
(m) starches;
(n) steroids;
(o) acridine;
(p) vitamins; and
(q) polyalkylene glycols.

52. The composition of Claim 38, wherein at least one nucleotide unit of said oligonucleotide is substituted with a conjugate group selected from the group consisting of:

(a) amino acids;
(b) peptides, polypeptides, and proteins;
(c) dipeptide mimics;
(d) sugars;
(e) sugar phosphates;
(f) neurotransmitters;
(g) hormones;
(h) poly (hydroxypropylmethacrylamide);
(i) polyethylene imine;
(j) dextrans;
(k) polymaleic anhydride;
(l) cyclodextrins;
(m) starches;
(n) steroids;
(o) acridine;
(p) vitamins; and
(q) polyalkylene glycols.

53. A method of inhibiting HIV protease function, comprising:

contacting an HIV genomic protease binding site with an oligonucleotide complementary to said HIV genomic protease binding site in an amount effective to inhibit HIV protease function.

54. A method of screening a compound for the ability to inhibit HIV protease, comprising:

contacting, in a first reaction, a predetermined amount of HIV protease with a predetermined amount of an oligonucleotide which binds HIV protease;

determining the amount of HIV protease bound by said oligonucleotide;

contacting, in a second reaction, said predetermined amount of HIV protease with said predetermined amount of an oligonucleotide which binds HIV protease and with a predetermined amount of said compound being screened for the ability to inhibit HIV protease; and

determining the amount of HIV protease bound by said oligonucleotide in said second reaction.

55. A method of detecting HIV infection in an individual comprising:

contacting a sample obtained from a person suspected of being infected with HIV with an oligonucleotide which binds to HIV protease; and

determining the amount of said oligonucleotide bound by HIV protease in said sample.

56. A method of treating HIV infection in a host, comprising:

administering to a host an oligonucleotide which inhibits HIV protease, said oligonucleotide being administered in an amount effective to treat HIV infection in a host.

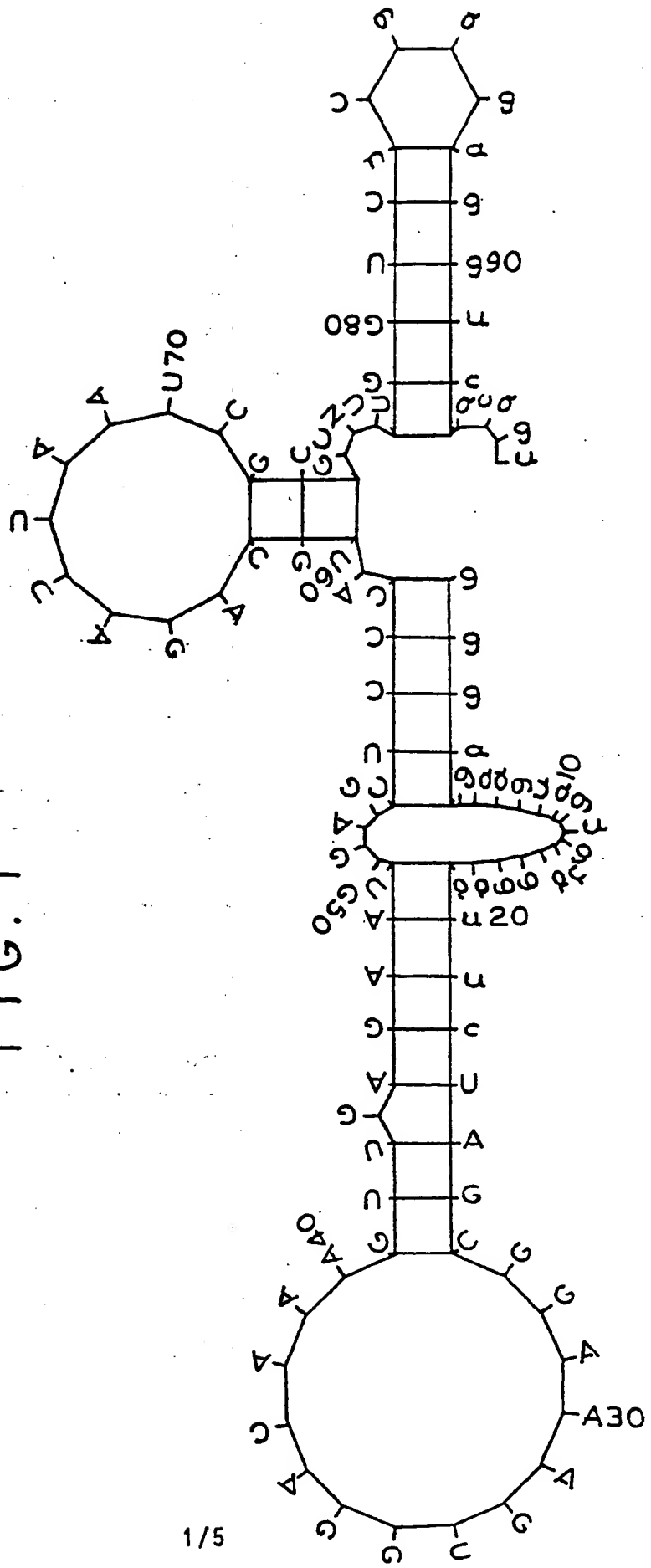


FIG. 1

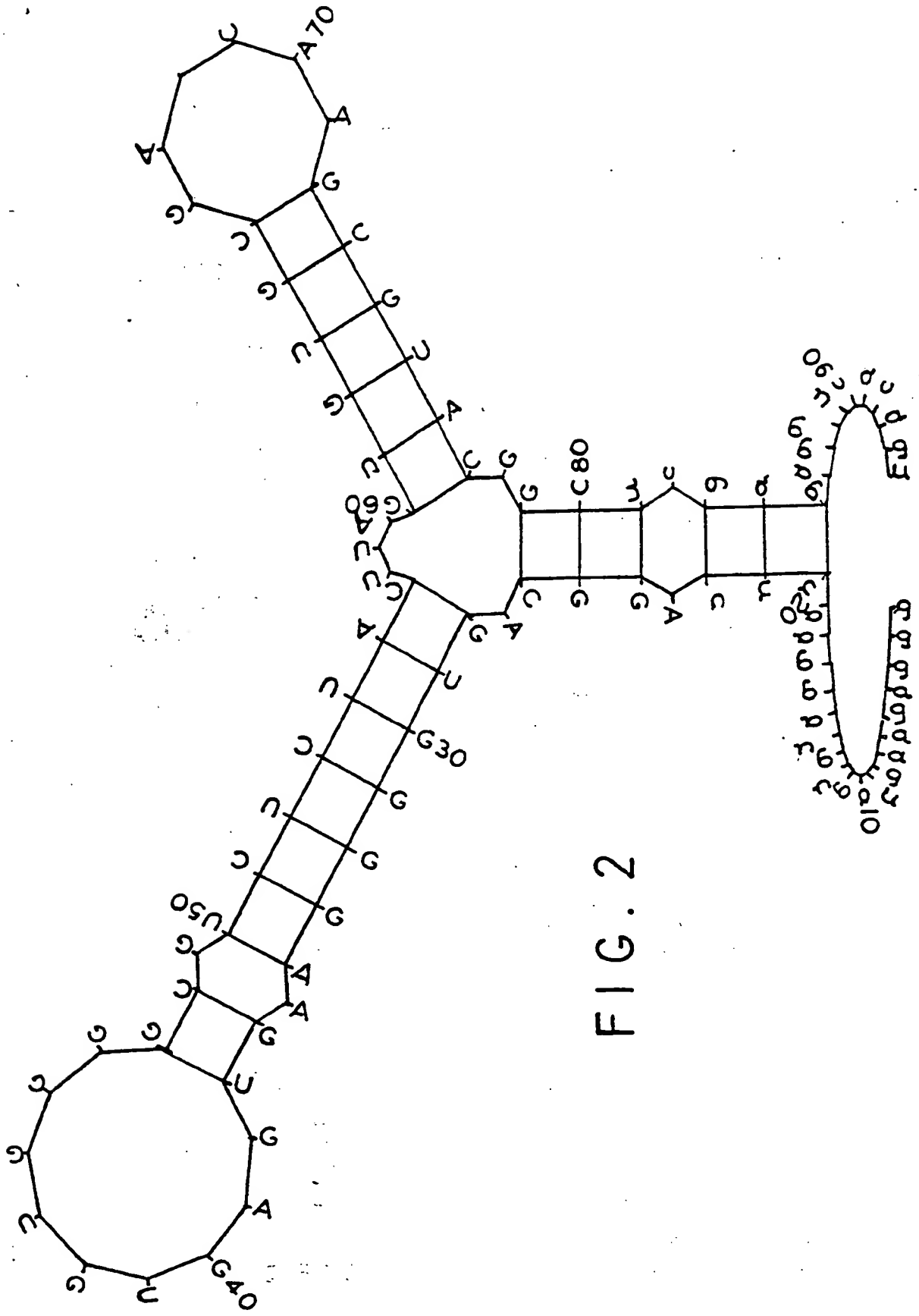


FIG. 2

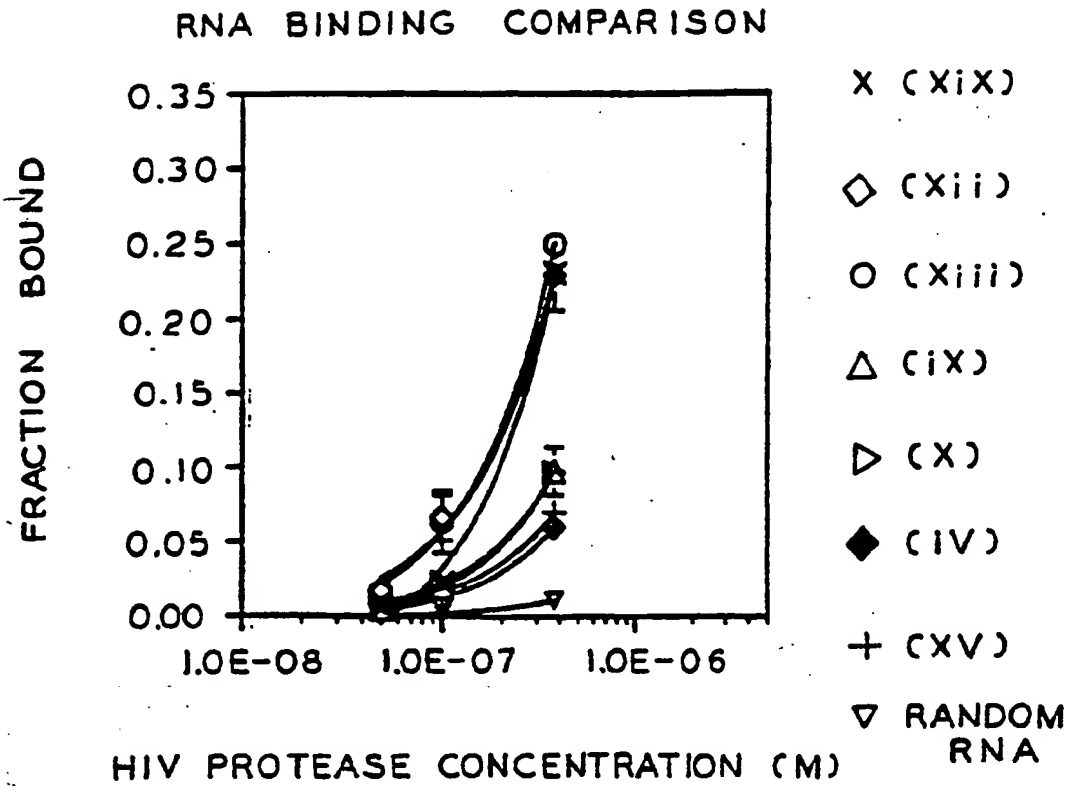

RNA BINDING COMPARISON
FRACTION BOUND
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1.0E-08
1.0E-07
1.0E-06
HIV PROTEASE CONCENTRATION (M)
X (XiX)
◇ (Xii)
O (Xiii)
△ (iX)
▷ (X)
◆ (IV)
+ (XV)
▽ RANDOM RNA

FIG. 4

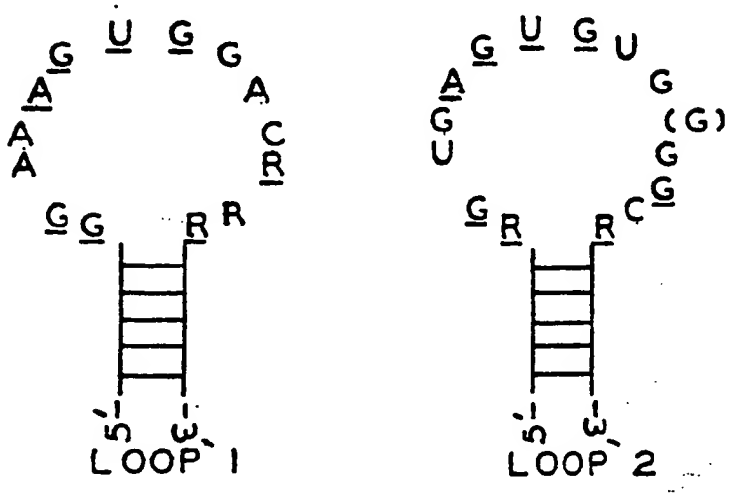

LOOP 1
LOOP 2

FIG. 3

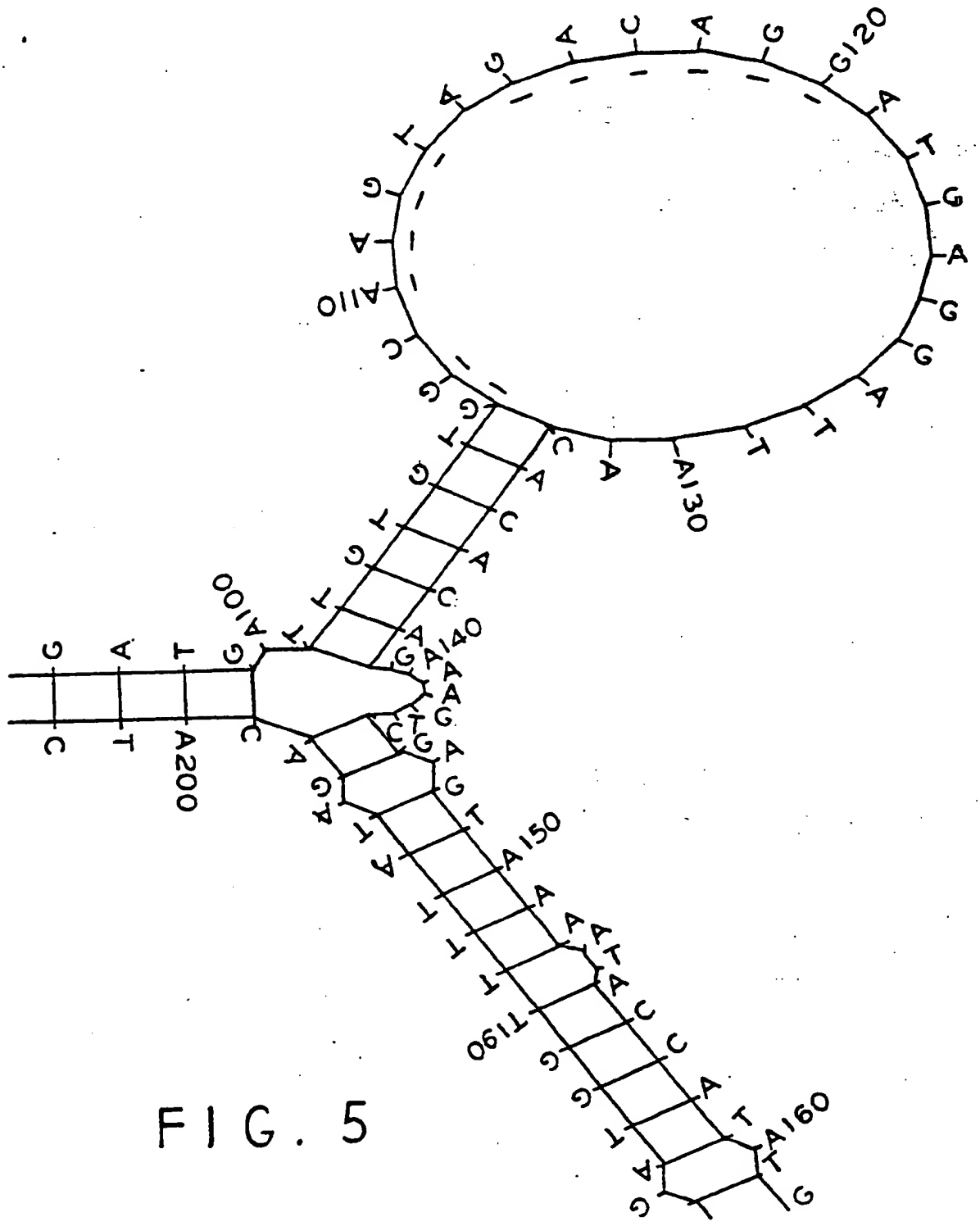
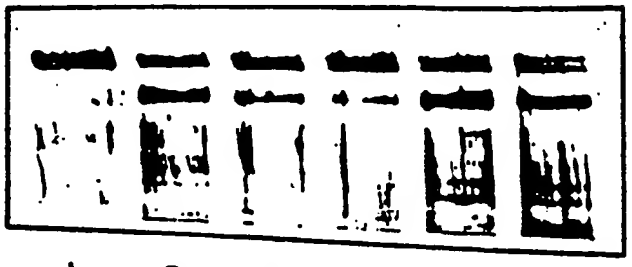


FIG. 5

SEQUENCE SPECIFIC
HIV PROTEASE INHIBITION

SUBSTRATE	+	+	+	+	+	+
PROTEASE	−	+	+	+	+	+
RANDOM OLIGO (nM)	−	−	−	−	100	5000
OLIGO (Xii) (nM)	−	−	40	100	−	−

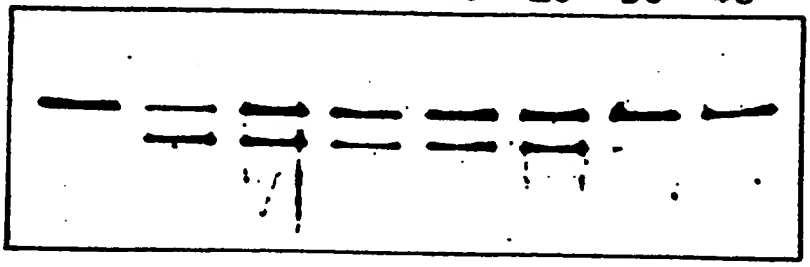


1 2 3 4 5 6

FIG. 6

TITRATION
HIV PROTEASE INHIBITION

SUBSTRATE	+	+	+	+	+	+	+	+
PROTEASE	−	+	+	+	+	+	+	+
OLIGO (nM)	−	−	5	10	15	20	30	40



1 2 3 4 5 6 7 8

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06456

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C12Q 1/00; C07H 21/02, 21/04; A61K 48/00

US CL :435/6; 514/44; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 514/44; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS; DIALOG DATABASES: BIOSIS PREVIEWS, MEDLINE, AIDSLINE, WORLD PATENT INDEX, CA SEARCH; GENBANK

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	"New England Biolabs 1990-1991 Catalog," published 1990 by New England Biolabs, Inc., page 76, see oligonucleotide #1235.	22, 24-28, 38, 40-44 ---------- 14,16-20, 30-32, 34-36
Y	Genomics, Volume 8, issued 1990, Jaenicke et al., "The Complete Sequence of the Human β-Myosin Heavy Chain Gene and a Comparative Analysis of Its Product," pages 194-206, see Figure 3, nucleotide numbers 443-446.	14, 22, 30, 38
A	AIDS Research and Human Retroviruses, Volume 8, Number 2, issued 1992, Debouck, "The HIV-1 Protease as a Therapeutic Target for AIDS," pages 153-164, see entire article.	1-56

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
01 AUGUST 1994	AUG 09 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOHNNY F. RAILEY II, PH.D. Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06456

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Pharmaceutical Research, Volume 9, Number 6, issued 1992, Mohan, "Anti-AIDS Drug Development: Challenges and Strategies," pages 703-714, see pages 705-706 especially.	1-56